Vertebroplasty, Kyphoplasty, Sacroplasty: Assessing Signals for Update

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1. Introduction

A Health Technology Assessment titled: ***Vertebroplasty, Kyphoplasty, Sacroplasty***, was published on November 5, 2010 by the Health Care Authority. Findings and Coverage Decision was adopted on March 18, 2011. The Committee's Coverage Decision is summarized below.

HTCC Coverage Determination

Vertebroplasty, Kyphoplasty and Sacroplasty are not covered benefits.

HTCC Reimbursement Determination

Vertebroplasty, Kyphoplasty and Sacroplasty are not covered benefits.

Committee Findings

Having considered the evidence based technology assessment report and the written and oral comments, the committee identified the following key factors and health outcomes, and evidence related to those health outcomes and key factors:

1. Evidence availability and technology features

The committee concludes that the best available evidence on Vertebroplasty, Kyphoplasty and Sacroplasty has been collected and summarized. Summary of committee considerations follows.

- The evidence based technology assessment report indicates that vertebral compression fractures and sacral insufficiency fractures occur, commonly as part of the natural disease progression of osteoporosis or osteopenia. Some patients with fractures are asymptomatic but others experience acute pain, loss of function, and decreased quality of life thought to be caused by the fracture.
- Vertebroplasty (PV), kyphoplasty (KP) and sacroplasty are all cementoplasty techniques that aim to relieve pain thought to be caused by the fracture by stabilizing the fractured bone(s). Vertebroplasty and sacroplasty are considered minimally invasive procedures and are usually performed using only local anesthesia or with conscious sedation. General anesthesia may be used. Kyphoplasty almost always requires general anesthesia and at least one overnight stay in the hospital. The patient must lie prone during all three procedures. Multiple levels can be treated during the same session. Patients are usually selected based on failure of conservative treatment or incapacitating pain. Alternatives include conservative management and surgical fixation, though invasive surgery may be problematic due to common comorbidities in the elderly and female population most often considered for this treatment.
- Despite increasing use of these procedures (rates of kyphoplasty doubled between 2001 and 205), the evidence for the procedure remains low and the efficacy, safety and economic impact are not well understood. Patients are generally elderly women with osteopenic fractures and most included studies focused on this population.
- The timing of intervention is an important consideration. Most patients are successfully treated with conservative care which resolves pain in 4 to 6 weeks and is generally recommended first. However, patients with acute fractures (less than six weeks) may be more likely to experience pain relief and the rapid recovery from debilitating pain is a primary treatment aim. Fracture age is difficult to determine as patients may have difficulty pinpointing the onset of pain and whether a certain event may be associated with the onset.

- In addition to typical complications from invasive procedures, cementoplasty techniques include risk of possible increase of subsequent compression fractures near a cemented vertebra due to increased rigidity of the treated vertebrae and risk of cement leakage.
- Evidence included in the technology assessment review was obtained through systematic searches of the medical literature for systematic reviews including meta-analyses, randomized controlled trials, observational studies, and economic studies. 11 RCTs, 23 Observational studies, and 3 economic studies met inclusion criteria and were included in the review. Overall strength of evidence from these studies was low to very low or inconclusive. Two RCTs compared vertebroplasty with sham procedure; three RCTs compared vertebroplasty to conservative care; one RCT compared kyphoplasty to conservative care; and one RCT compared kyphoplasty and vertebroplasty.
    - The evidence based technology assessment report identified 4 clinical guidelines; there is no National Coverage decision on vertebroplasty, kyphoplasty or sacroplasty.
    - The committee also reviewed information provided by the state agencies, and public members; and heard comments from the evidence reviewer, clinical expert, HTA program, agency medical directors and the public.

2. Is it safe?

The committee discussed multiple key factors and health outcomes that were important for consideration in their overall decision on whether the technology is safe. Key factors to the committee's conclusion include:

- The evidence-based technology assessment report concluded that the overall strength of evidence for safety is low for vertebroplasty and kyphoplasty and very low for sacroplasty and evidence based estimate of effect are uncertain. While it appears that rates of serious complications are low for vertebroplasty and kyphoplasty, studies with long-term (> 5 year) follow-up are few and comparative studies, especially RCTs, may have too few patients to detect more rare but serious outcomes. Primary safety outcomes reported include rates of new fracture, cement leakage, pulmonary cement embolism, and mortality related to vertebroplasty and kyphoplasty.
- *New fractures (adjacent or non-adjacent)* – in comparative studies, rates of new fractures were up to 30% at 12 months, with no consistent pattern across studies of increased fracture rates for any one treatment (vertebroplasty, kyphoplasty, or conservative treatment). One RCT reported that the distribution of fracture location (adjacent or non-adjacent) was similar for vertebroplasty and non-surgical patients. Systematic reviews, incorporating information on longer-term follow-up with a large (pooled) number of patients in case series, suggest that rates of new fracture may be slightly higher in vertebroplasty (18-19% of patients, 16-21% of vertebral levels) than kyphoplasty (7-17% of patients, 11-13% of levels). One systematic review concluded that the proportion of new fractures that were in adjacent vertebrae was higher for kyphoplasty (75%) than for vertebroplasty (52%).
- *Cement leakage* – in comparative studies, rates of cement leakage (largely asymptomatic) approached 80% for vertebroplasty and 50% for kyphoplasty, with some evidence that leakage is more common with vertebroplasty than with kyphoplasty. Systematic reviews also suggest that leakage is more common in vertebroplasty (19.7% - 79.0% of levels treated) than in kyphoplasty (0.51% - 11.2%), and that rates of symptomatic leakage are quite low (0.5%-1.6%of levels treated for vertebroplasty and 0% - 0.3% for kyphoplasty).
- *Pulmonary cement embolism* – as a result of differential surveillance in RCTs, nonrandomized studies, and case series, rates vary widely across studies. One RCT using computed tomography to detect emboli reported that 26% (15/54) of vertebroplasty patients had a cement embolism, all of

which were asymptomatic. No incidents of symptomatic embolism were reported in comparative studies. A systematic review of cement embolism reported rates of 1.6% for asymptomatic PCE and 1.1% for symptomatic PCE (all but one of the case series included in the review were of vertebroplasty patients).

- *Mortality* – systematic reviews (based on case series) estimate mortality rates at 2.1% for vertebroplasty and 2.3%-3.2% for kyphoplasty; the timing of mortality was not reported. Perioperative mortality rate for kyphoplasty was .01% across 11 case series. Since the majority of patients receiving these procedures are elderly and/or have malignant disease, the extent to which mortality can be attributed to the procedures is unclear.
- *Sacroplasty* – the evidence based technology assessment report indicates that the overall strength of evidence about safety of sacroplasty is very low, and all data are from case series. Cement leakage was the only reported complication and occurred in 7 of 34 (20.6%) patients across four case series.

3. Is it effective?

The committee discussed multiple key factors and health outcomes that were important for consideration in their overall decision on whether the technology is effective. Key factors to the committee's conclusion include:

- Vertebroplasty
    - *Pain Relief* – the evidence based technology assessment report concluded that the overall strength of evidence about effectiveness of vertebroplasty to reduce/relieve pain is *low*; any effect estimate is uncertain and may change with additional research. The low strength of evidence and lack of ability to estimate effect based on evidence is due to the limitations of the studies and that the studies reported differing outcomes (some studies showed benefit others did not). The RCTs were limited to patients with osteoporotic fractures and evaluated short-term effects (≤12 months). Two sham-controlled RCTs demonstrated no difference in pain relief (up to 1month in one study and 6 months in the other), though both studies were limited in power to detect differences in the proportion of patients with clinically meaningful improvement. Another RCT demonstrated statistically significant improvement in pain scores sustained to the 12-month follow-up compared to conservative care and included more patients but was not blinded and did not include a placebo comparison. Two small RCTs reported no advantage for vertebroplasty over 2 weeks or 12 months. Four nonrandomized studies with follow-up up to one year found that vertebroplasty was more effective in reducing pain than conservative medical treatment at up to approximately six months, but no difference at one year.
    - *Function and quality of life* – the evidence based technology assessment report concluded that the overall strength of evidence about effectiveness of vertebroplasty to improve patient function or quality of life is *low*; any effect estimate is uncertain and may change with additional research. One larger RCT demonstrated that PV was more effective than conservative treatment in improving functioning as measured by the QualEffo and RDQ, although it is possible that early differences in improvement diminish over time. Two small RCTs found comparable improvements in function over 2 weeks and 12 months for vertebroplasty and non-surgical patients. In 4 non-randomized studies, vertebroplasty showed superior effectiveness in improvements in functioning and quality of life in the first 3-6 months was followed by equivalence at one year.
- Kyphoplasty

  - *Pain Relief* – the evidence based technology assessment report concluded that the overall strength of evidence about effectiveness of kyphoplasty to relieve/reduce pain is very low; any effect estimate is uncertain and may change with additional research.
  - Only one RCT compared kyphoplasty with conservative treatment, reporting that while pain was reduced more rapidly in kyphoplasty patients, this advantage over conservative treatment was diminished by the one-year follow-up. Because of the paucity of RCTs comparing kyphoplasty to conservative treatment, the overall strength of evidence is low and effect estimates may change with additional research. In two non-randomized studies, kyphoplasty reduced pain more than conservative medical treatment for periods up to 3 years.
  - *Function and quality of life* – the evidence based technology assessment report indicated that it is uncertain whether kyphoplasty improves patient functioning and quality of life. In these two studies, kyphoplasty improved a limited set of functional outcomes more than conservative medical treatment.
- Sacroplasty
  - There is no evidence of efficacy for sacroplasty. Very limited data from 9 case series (N = 141 total patients) is available, the case series showed pain relief with sacroplasty; but the absence of comparative studies, small patient size do not permit an evidence based conclusion.

4. Is it cost-effective?

The committee discussed multiple key factors that were important for consideration in their overall decision on whether the technology has value and is cost-effective. Summary of committee considerations follows:

- The evidence based technology report summarized three economic studies, however, because the evidence about efficacy, effectiveness, and safety is low to very low and evidence based estimates of effect are uncertain; conclusions about cost effectiveness are premature. No cost studies were conducted with U.S. data, the cost effectiveness of vertebroplasty, kyphoplasty or sacroplasty in a US setting is unknown.
- The economic impact of complications, reoperation, or revision following vertebroplasty, kyphoplasty, or sacroplasty is unknown.
- Washington state agency utilization and cost information indicates that the single agency that reimburses (UMP) for these procedures expended $868,543 in the last four years, with an average cost of $10,837; and both procedure volume and costs are rising annually.

5. Medicare Decision and Expert Treatment Guidelines

The committee deliberations included a discussion of National Medicare Decisions and expert treatment guidelines, and an understanding that the committee must find substantial evidence to support a decision that is contrary. RCW 70.14.110.

The Committee reviewed and discussed the expert guidelines as identified and reported in the technology assessment report. Overall, the clinical guidelines and Medicare coverage decisions included in the evidence report and the AAOS guideline published subsequent either do not cite evidence or rely on evidence assess as low or very low quality or consensus statements.

- Centers for Medicare and Medicaid Services (CMS) have no published National or Local coverage determinations for vertebroplasty, kyphoplasty or sacroplasty.

- The evidence based technology assessment report identified three guidelines on vertebroplasty, kyphoplasty and/or sacroplasty, although no guideline specifically addressed the procedures for osteoporosis or malignancy – the studied indications.
    - Two guidelines mentioned vertebroplasty and kyphoplasty as part of the assessment and management of spinal cord compression and chronic pain and indicate they may be considered.
        - Institute for Clinical Systems Improvement (ICSI), 2008
        - National Collaborating Centre for Cancer, National Institute for Health and Clinical Excellence (NICE), 2008
    - American Society of Interventional and Therapeutic Neuroradiology, Society of Interventional Radiology, American Association of Neurological Surgeons/Congress of Neurological Surgeons, and American Society of Spine Radiology -- A consensus statement on percutaneous vertebral augmentation was developed: "It is the position of the Societies that vertebral augmentation with vertebroplasty or kyphoplasty is a medically appropriate therapy for the treatment of painful vertebral compression fractures refractory to medical therapy when performed for the medical indications outlined in the published standards1-3."
    - American Association of Orthopaedic Surgeons (AAOS) -- recommend against vertebroplasty for patients who present with an osteoporotic spinal compression fracture on imaging with correlating clinical signs and symptoms and who are neurologically intact. *Strength of Recommendation: Strong*. Kyphoplasty is an option for patients who present with an osteoporotic spinal compression fracture on imaging with correlating clinical signs and symptoms and who are neurologically intact. *Strength of Recommendation: Weak.*

2. Purpose of Report

The purpose of this literature update is to determine whether or not there is sufficient evidence published after the original report to conduct a re-review of this technology based on the presence of preset signal criteria. The key questions included the following:

Key question 1

What is the evidence of efficacy and effectiveness of vertebroplasty, kyphoplasty or sacroplasty? Including consideration of:

a. Short-term and long-term outcomes
b. Impact on function, pain, quality of life
c. Other reported measures including: use of pain medications and opioids, return to work

Key Question 2

What is the evidence of the safety of vertebroplasty, kyphoplasty or sacroplasty? Including consideration of:

a. Adverse events type and frequency (mortality, major morbidity, other)
b. Revision/re-operation rates (if not addressed in efficacy)

Key Question 3

What is the evidence that vertebroplasty, kyphoplasty or sacroplasty has differential efficacy or safety issues in sub populations? Including consideration of:

a. Gender
b. Age

c. Psychological or psychosocial co-morbidities
d. Diagnosis or time elapsed from fracture
e. Other patient characteristics or evidence based patient selection criteria
f. Provider type, setting or other provider characteristics
g. Payer/beneficiary type: including worker's compensation, Medicaid, state employees

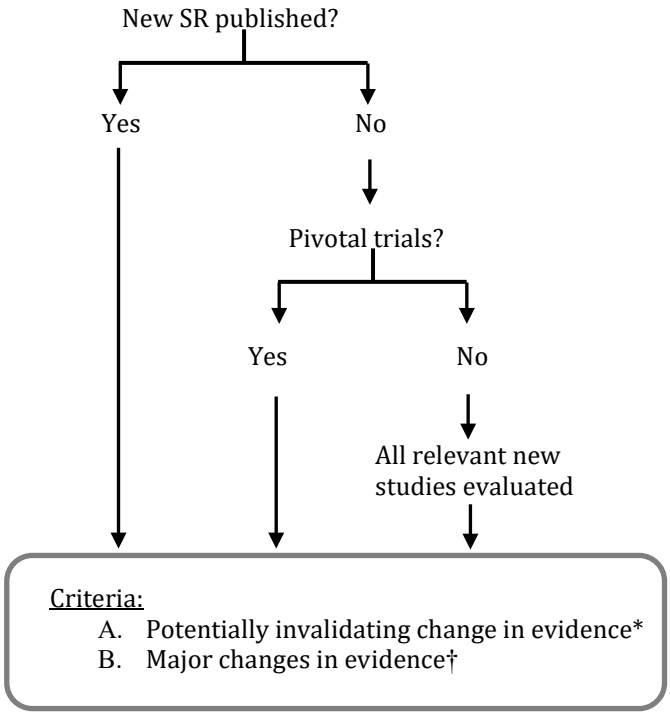
Key Question 4
What is the evidence of cost implications and cost-effectiveness of vertebroplasty, kyphoplasty and sacroplasty? Including consideration of:

a. Costs (direct and indirect) in the short term and over expected duration of use
b. Revision/re-operation (if not addressed in efficacy)

3. Methods

To determine the need for systematic review update, the following algorithm was followed:

Figure 1. Algorithm of the modified Ottawa Method of Identifying Signals for SR Updates



*A-1. Opposing findings: Pivotal trial or SR including at least one new trial that characterized the treatment in terms opposite to those used earlier

A-2. Substantial harm: Pivotal trial or SR whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision making (e.g., the risk of harm outweighs the benefits, identification of new serious adverse events)

A-3. Superior new treatment: Pivotal trial or SR whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm

†B-1. Important changes in effectiveness short of "opposing findings"

B-2. Clinically important expansion of treatment (e.g., to new conditions or subgroups of subjects or additional FDA indications)

B-3. Clinically important caveat

B-4. Opposing findings from discordant meta-analysis or nonpivotal trial

Additional general criterion to consider:

- Quantitative signals include a change in statistical significance in which a statistically significant result in the original report is now NOT statistically significant or vice versa which is substantial and/or a change in effect size of at least 50%.

3.1 Literature Searches

We conducted a limited electronic literature of Medline for systematic reviews with meta-analysis during the period August 26, 2016 to March 6, 2020 using terms used for the original report. A previous signal search was completed in December of 2016, which conducted a similar search for systematic reviews published between March 1, 2010 and November 26, 2016. Appendix A includes the search methodology and results for the 2020 signal update. In addition, we searched the FDA website to determine if there was approval of new devices or indications for vertebroplasty, kyphoplasty or sacroplasty (see Appendix E).

3.2 Study selection

We sought systematic reviews of randomized controlled trials (RCTs) of efficacy and safety with meta-analysis that included articles that met inclusion and exclusion criteria similar to the original report. In addition, we sought systematic reviews reflecting updates or new advances for the technology or safety. Secondary to the large number of citations returned, we focused on screening only systematic reviews and meta-analyses of RCTS published between 2017 and 2020. We chose to summarize systematic reviews that were the most comprehensive and of high quality based on an AMSTAR 2 evaluation. With the exception of safety specific SRs and SRs of VKS for malignancy-related vertebral fractures, only systematic reviews of RCTs were included. RCTs not included in the summarized systematic reviews that met inclusion criteria were also abstracted and evaluated for risk of bias. AMSTAR 2 evaluations for the included SRs and a risk of bias evaluation for the summarized RCTs can be found in Appendix F.

4. Results

4.1 Search

There has been a substantial increase in the number of randomized control trials (RCT) related to vertebral augmentation. Subsequent to the publication of the original 2010 HTA report, which contained 7 RCTs, 17 additional RCTs relevant to the Key Questions have been published. Thus, a total of 24 RCTs now comprise the evidence base for efficacy. (Table 1) Since the publication of the original 2010 HTA report, the total number of potentially relevant citations has changed from 205 in 2010 to 397 for this report, with the actual number of potentially relevant citations likely to be higher as the 2016 and 2020 update searches were limited by publication type.

Table 1. Count of RCTs on cement augmentation

	2010 HTA	New RCTs from Signal Updates	Total RCTS (N=)
VP vs. Sham	2 RCTs	3 RCTs	5 RCTs (N=541)
VP vs. CMT	3 RCTs	5 RCTs	8 RCTs (N=1136)
KP vs. Sham	0	0	0
KP vs. CMT	1 RCT	2 RCTs	3 RCTs (N=496)
VP vs. KP	1 RCT	6 RCTs	7 RCTs (N=968)
VP vs. facet injection	0	1 RCT	1 RCT (N=217)
Sacroplasty	0	0	0
TOTAL	7	17	24

The 2016 signal search identified 3 systematic reviews (SRs), 3 RCTs, and 3 cost-effectiveness studies (see Appendix G for citations of studies included in the 2016 signal update). All three of the RCTs not previously included in a SR in the 2016 signal update report, are now included in the summarized Buchbinder 2018 SR identified by the 2020 signal update search.

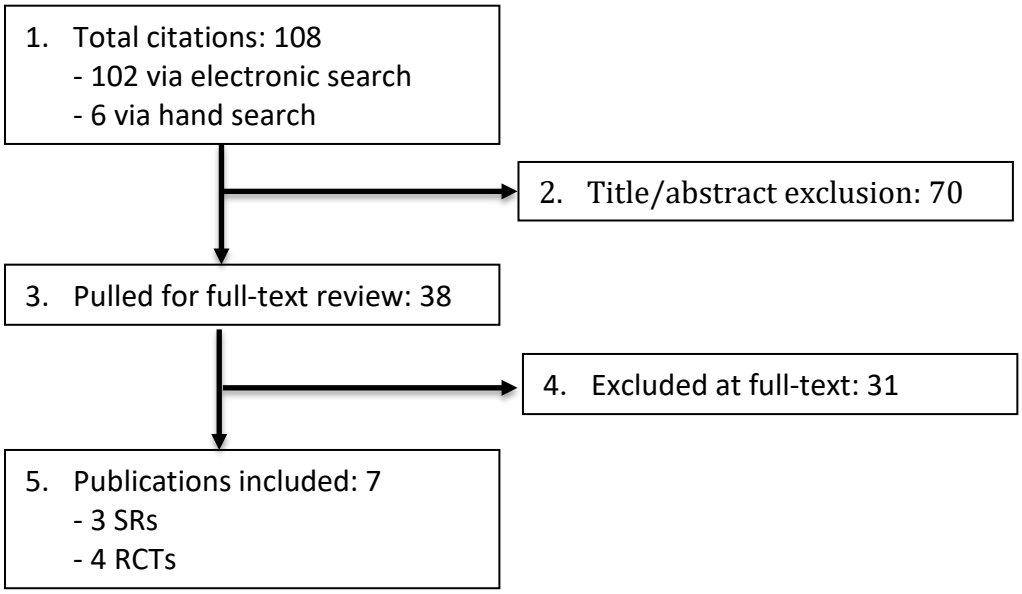
After deduplication and the addition of a further 6 publications found via handsearching, the 2020 signal update search identified a total of 108 publications (Appendix A for search strategy). Of these, 70 publications were excluded at the title abstract level, leaving 38 potentially relevant publications for full text review. At the full text level, 31 publications were excluded, leaving 7 publications (3 SRs[2,14,24] and 4 RCTs[10,18,20,21]) to be summarized for this signal update (Figure 2). Of note, although one SR[22] of sacroplasty was excluded at full-text due to lack of RCT data, it appears that 2 non-randomized comparative cohort studies[12,31] are included in this SR that may meet inclusion criteria for effectiveness of sacroplasty.

The most comprehensive SR included RCTs of PV and provided data for KQ 1, 2, and 3. While the focus of this signal update was to include SRs of RCTs, we chose to include two SRs of non-RCT data for areas where evidence was limited. One SR of non-RCT data analyzed PV and KP for malignancy-related vertebral fractures and provided data for KQ 1 and 2, and another SR of non-RCT data analyzed safety (mortality) data (KQ2) related to VP and/or KP for osteoporotic vertebral compression fractures.

Across the four RCTs identified that were not included in an SR, one provided data for KQ1 and KQ2, two provided data for KQ1 only, and the final was a safety specific publication (KQ2) associated with the previously identified VERTOS IV trial. No new studies addressing KQ4 were identified.

A table of new FDA approved devices is found in Appendix E. All were considered to be variations of existing devices versus new devices and were approved via the 510(k) process. In May 2015, Stryker received 510(k) approval to expand the indications for use of VertaPlex HV Radiopaque Bone Cement to pathological fractures of the sacral vertebral body.

Figure 2. Flow chart showing results for 2020 signal update search results for systematic reviews



RCT = randomized control trial; SR = systematic review

4.1 Risk of bias evaluation

Buchbinder 2018 SR assessed the risk of bias of their 21 included studies across eight domains. 62% of studies were found to be at low risk of bias for randomization, 43% for allocation concealment, 19% for blinding of participants and personnel, 34% for blinding of self-reported outcomes assessment, 10% for blinding of objective outcomes assessment (e.g. radiographic outcomes), 24% for attrition, 19% for selective reporting of outcomes, and 53% for other bias. Notably, 79% of studies were found to be at high risk of bias for blinding of objective outcomes assessment, and 48% of studies for blinding of participants and personnel and blinding of self-reported outcomes assessment. The authors did not provide an overall risk of bias rating for each of the included studies.

Across the four newly identified RCTs that were not included in the Buchbinder 2018 systematic review, all were considered to be at high risk of bias (poor quality), with the exception of one trial which was determined to be at low risk of bias. The trial considered to be at low risk of bias is a safety specific publication related to the VERTOS IV trial; the parent publication for this trial was included in the Buchbinder 2018 systematic review and received mostly low risk of bias judgements across the domains. Across the three trials considered to be at high risk of bias, methods were generally poorly reported; none of these trials described allocation, blinding, or attrition. (Appendix F)

4.2 Identifying signals for re-review

Tables 1-3 in Appendix C show the original key questions, the conclusions of the original 2010 HTA report, the 2016 signal update conclusions, the new sources of evidence since the last signal update, and the corresponding new findings and recommendations of Aggregate Analytics, Inc. regarding the need for update.

5. Summary of Results and Conclusions

There has been a substantial increase in the number of publications related to vertebral augmentation and sacroplasty in the past decade as noted in section 4. The RCT evidence base related to vertebral augmentation has expanded. Subsequent to the original 2010 HTA, which contained 7 RCTs[3,15,16,19,23,27,29], 17 additional RCTs[1,4-9,11,13,17,18,20,21,25,26,28,30] relevant to the Key Questions have been published. A total of 24 RCTs now comprise the evidence base for efficacy. Additions to the evidence base for effectiveness from nonrandomized studies was not explored for this signal update.

Overall, the addition of new RCT data suggests that for some outcomes and treatment comparisons, there may be some change from no consistent statistically significant difference to a difference favoring percutaneous vertebroplasty (PV) that may be clinically meaningful (Criterion B-1) as noted below and in the Appendix C tables. One RCT with a new comparator (facet injection) was identified. No new summary of RCT data on mortality was identified in SRs, however discrepant results from a recent SR of observational studies comparing PV or kyphoplasty (KP) versus conservative medical treatment (CMT) and one identified in the 2016 signal report should be explored in greater depth and this section of the report could be updated (Criteria A-2, B-1). The signal update methods may not fully capture observational studies specifically designed to evaluate safety, particularly for rare outcomes or over the long-term unless they are captured in SRs.

This signal update focuses on the highest quality evidence from RCTs and SRs but does not formally assess the overall strength of evidence (SOE) on primary outcomes across studies as would be done in a formal HTA. In the 2010 report, the overall SOE for most outcomes was low or very low (i.e. insufficient). It is

likely that the addition of evidence from the recently published RCTS would result in an upgrade of SOE for many outcomes and comparisons. Comparative observational studies that may provide additional information on the benefits and risks of augmentation for less common pathologic, malignancy-related fractures (for which RCTS may be challenging) and for sacroplasty may not have been captured. Economic evaluations in and of themselves do not signal the need for a re-review, however this section of the report could be updated with the economic studies identified in the 2016 signal report.

Vertebroplasty (PV)

- A total of five RCTs (3 new since the 2010 HTA) comparing **PV with sham** have been identified.
    - Updated pooled estimates from one high quality SR suggests that more PV patients experience clinically meaningful pain relief **versus sham** at 12 months. The 2016 signal report noted a shift from no statistical difference between groups in the original HTA to marginally significant (lower bound for 95% CIs ranged from 0.99 to 1.12) at 1, 3 and 6 months. This change in evidence from no difference to a difference favoring PV suggests that re-review may be of value (Criterion B1).
    - No clinically meaningful between-group mean differences for VAS pain, RDMQ, QUALEFFO, EQ-5D were seen in updated meta-analyses with the new trials. Statistical significance was reached only at 1 month for VAS pain and RMDQ. These findings do not change the conclusions of the previous report (criteria A-1 or A3) nor provide major changes in the evidence for these analyses (Criteria B1-4).
    - The addition of the new trials may change the overall SOE for outcomes compared with the 2010 HTA if a re-review is done.
- A total of eight unblinded RCTs (5 new since the 2010 HTA) comparing **PV with conservative medical care** (usual care) have been identified.
    - Updated pooled estimates from one high quality SR suggests that PV was more consistently associated with improved pain and function compared with CMT and that some effect sizes may be clinically meaningful. This is a change from the 2010 HTA and 2016 signal report which found no consistent statistically significant differences to a difference favoring PV that may be clinically meaningful when compared with CMT, suggesting that re-review may be of value (Criterion B1).
    - The addition of the new trials may change the overall SOE for some compared with the 2010 HTA if a re-review is done.
- One new RCT comparing **PV with facet join injection** was identified. This comparator was not identified in the 2010 HTA.
    - Statistically significant improvement in pain and function which may be clinically relevant were only seen at 1-2 weeks. There were no differences between groups in the occurrence of new radiographic fractures.
    - The findings from a single RCT of this comparison do not meet the criteria that would trigger an updated report (Criteria A-3, B1-4).
- Safety:
    - Pooled RCT evidence from one high quality SR showed no statistically significant differences between PV versus sham or CMT in new clinical or radiographic fractures or serious adverse events. New RCTs included in the SR do not change the conclusions from the previous report (criteria Criterion A-2) for these outcomes.
    - Conclusions regarding mortality from SRs of observational studies **of PV or KP** identified in the 2016 and this current signal report differ; the most recent SR suggests mortality is lower with **PV or KP** while the one identified in 2016 reported no difference compared

with CMT. Discrepancies between these reviews should be explored in greater depth and this section of the report could be updated (Criteria A-2, B-1).

- Differential efficacy: One high quality SR evaluated heterogeneity of treatment effect (i.e. interaction) by fracture age (acute vs. subacute) for pain, disability and EQ-5D. Tests for interaction were not statistically significant, however definitions for age varied across studies and sample sizes may not have been adequate to detect a difference. Findings from the systematic review do not change the conclusions from the previous report however data could be used to update this section.
- Cost-effectiveness: Findings of economic studies do not change the conclusions from the previous report. They could be used to update this section if a re-review is done
    - A 2014 HTA (included in 2016 signal update) reported that no definitive conclusion on the cost-effectiveness of PV can be provided given the uncertainty in the evidence base.
    - In patients with pathologic fractures, a 2016 Ontario HTA suggests that compared with nonsurgical management, **PV and KP** may be cost-effective compared with usual care at commonly accepted willingness to pay thresholds.

Kyphoplasty (KP)

- A total of three unblinded RCTs (2 new) comparing **KP with conservative medical care** (usual care) in patients with osteoporotic fractures have been identified.
    - The three RCTs together suggest that KP may be associated with improved pain and function versus CMT but clinical importance is unclear; the two new poor quality trials are not considered pivotal and do not change the conclusions from the previous report (criteria A-1 or A3), nor provide major changes in the evidence (criteria B1-B4).
- An RCT identified in the 2016 signal report was included together with observational studies in a recent SR in patients with pathological (malignancy-related) fractures.
    - In the RCT, KP was associated reduced pain, disability and use of medication; SF-36 PCS and MCS scores were improved following KP vs. CMT at 1 month.
    - The SR presented only single arm data for PV and KP with no comparison to other treatments and suggest improved pain and function.
    - These data do not change the conclusions from the previous report (criteria A-1 or A3), nor provide major changes in the evidence (criteria B1-B4). They could be used to update this section if a re-review is done.
- Safety: Data on safety were poorly reported in studies comparing KP with CMT specifically; they do not change the conclusions from the previous report for this comparison (criteria Criterion A-2). (See previous discussion of findings from SRs of observational studies on mortality.)
- Cost-effectiveness: Findings of economic studies do not change the conclusions from the previous report (criteria A-1 or A-3), nor provide major changes in the evidence (criteria B-1). They could be used to update this section if a re-review is done.
    - In patients with osteoporotic fractures, two new cost-utility studies identified in the 2016 signal update suggest that KP may not be cost-effective versus CMT. One concluded that no definitive conclusion on the cost-effectiveness can be provided given the uncertainty in the evidence base.
    - In patients with pathologic fractures, a 2016 Ontario HTA suggests that compared with nonsurgical management, **PV and KP** may be cost-effective compared with usual care at commonly accepted willingness to pay thresholds.

Vertebroplasty(PV) versus Kyphoplasty (KP)

- A total of seven RCTs (6 new) compared PV with KP. The focus of the 2010 HTA was on evaluation of the efficacy and effectiveness of each of these individually versus sham or other appropriate comparators. Comparison of PV with KP was not of primary importance.
- Pooled analyses in one high quality SR that included 5 new RCTs found no difference between VP and KP on improvement for pain, function (ODI) or EQ-5D at any time point.
- The SR reported no differences between PV and KP in radiographic fractures (2 trials) or in serious adverse events (1 trial). One SR of observational studies on malignant fractures found cement leakage much more common with PV than with KP.
- Based on the SR, synthesized results that include the new trials are consistent with findings in the original HTA. No update of this section is needed (criteria A1, B1-B4).
- Strength of evidence (SOE) may change for outcomes based on new RCTs.

Sacroplasty

- There is no new RCT evidence on sacroplasty. The two SRs identified reported only single arm results for sacroplasty and were excluded at full text, however two comparative observational studies were cited in these SRs which could be evaluated if a re-review is done. No comparative studies were identified in the 2010 HTA or the 2016 signal update. There are no major changes in the evidence for efficacy (criteria B1-B4).

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APPENDIX A. SEARCH STRATEGIES

Appendix Table A1: PubMed search strategy and results

Search number	Query	Results
#1	(((vertebroplast* OR kyphoplast* OR sacroplast* OR vesselplast* OR skyphoplast* OR vertebral augmentation) NOT (cadaver*)) NOT (sheep)) AND (("2016/08/26"[Date - Publication] : "3000"[Date - Publication]))	104 (102 after deduplication)

Filters: Abstract, Meta-Analysis, Randomized Controlled Trial, Systematic Reviews
Search date: 03/06/20

APPENDIX B. SUMMARY OF INCLUDED SYSTEMATIC REVIEWS AND RCTS

Appendix Table B1. Summary of systematic reviews included for efficacy and safety

Assessment (year) Search dates	Purpose	Condition	Treatments vs. controls	Primary Outcomes	Evidence-base Used	Primary Conclusions
Buchbinder 2018 Date Accessed: 15 November 2017	To update the available evidence of the benefits and harms of vertebroplasty for treatment of osteoporotic vertebral fractures.	Osteoporotic VCFs	PV vs. sham, CMT, KP, or Facet joint injection	Pain, disability, disease-specific and overall health-related quality of life, patient-reported treatment success, new symptomatic vertebral fractures, serious adverse events	**PV vs. sham:** 5 RCTs (n=541) **PV vs. CMT:** 8 RCTs (n=1136) **PV vs. KP:** 7 RCTs, 1 quasi-RCT (n=968) **PV vs. Facet joint injection**: 1 RCT (n=217)	**PV vs. sham (efficacy):** No statistically significant difference and MCID* between groups at 1 to 2 weeks and 3, 6, 12, and 24 months. Only slight statistically significant (clinically unimportant) difference between groups in pain (VAS: 5 trials; n=535, MD -0.73; 95% CI -1.18 to -0.28) and disability (RMDQ: 4 trials; n=472, MD -1.50, 95% CI -2.61 to -0.38) at one month. Reported proportion of patients reporting their pain improvement by "clinically important" amount† at 1 month (3 trials; RR 1.53, 95% CI 0.99 to 2.36); 3 months (2 trials; RR 1.60, 95% CI 1.12 to 2.30); 6 months (2 trials; RR 1.38, 95% CI 1.02 to 1.87); 12 months (2 trials; RR 1.29, 95% CI 1.06 to 1.58). No statistically or clinically important differences were identified at 1 to 2 weeks (2 trials) or 24 months (1 trial) No statistically significant differences between groups for overall quality of life improvement for QUALEFFO and RMDQ at any timepoint. **PV vs. CMT (efficacy):** PV had greater improvement in mean pain at 1 to 2 weeks (6 trials; n=627, SMD -

Assessment (year) Search dates	Purpose	Condition	Treatments vs. controls	Primary Outcomes	Evidence-base Used	Primary Conclusions
						1.33, 95% CI -2.26 to -0.39); 1 month (3 trials; n=384, SMD -2.06, 95% CI -3.35to-0.76); 3 months (6 trials; n=627, SMD -1.18, 95% CI -1.95 to -0.40); 6 months (5 trials; n=573, SMD -1.05, 95% CI -1.82 to -0.28); 12 months (6 trials, n=612, SMD -1.02, 95% CI -1.74 to -0.30), but no statistically significant difference between groups at 24 months. PV had greater improvement in disability (RMDQ) at 1-2 weeks (5 trials; n=494, SMD -2.06, 95% CI -3.28 to -0.83); 1 month (3 trials; n=378, SMD 1.52, 95% CI -3.00 to -0.04); 3 months (4 trials; n=460, SMD -2.76, 95% CI -4.65 to -0.87); 6 months (4 trials; n= 461, SMD -1.84, 95% CI -3.37 to -0.30), 12 months (4 trials; n=455, SMD -1.59, 95% CI -2.79 to -0.38), and 24 months (1 trial, n=77, SMD -5.65, 95% CI -6.67 to -4.63) PV had greater improvement in quality of life measurement (EQ-5D at 1-2 weeks (1 trial; n=183, MD 0.08, 95% CI 0.00 to 0.15); 1 month (1 trial; n=183, MD 0.09, 95% CI 0.01 to 0.16); 3 months (2 trials; n=215, MD 0.07, 95% CI -0.02 to 0.15). No statistically significant differences between groups reported between 6 – 12 months or osteoporosis-specific quality of life at any time point measured by QUALEFFO.

Assessment (year) Search dates	Purpose	Condition	Treatments vs. controls	Primary Outcomes	Evidence-base Used	Primary Conclusions
						PV vs. sham or CMT (safety): More new clinically apparent vertebral fractures up to 12 and 24 months in the PV vs. the sham/CMT group but the difference was not statistically significant; no between-group differences in the number of new radiographic vertebral fractures at 12 or 24 months or in the number of other serious adverse events. **PV vs. KP:** No statistically significant between-group differences in pain, disability, and quality of life improvement at any timepoints, or new clinical radiographic vertebral fractures at 12 and 24 months or adjacent vertebral fractures up to 6 months. **PV vs. Facet Joint Injection:** Statistically significant difference between groups only at one week (pain MD 1.61, disability MD -3.42). No statistically significant difference between groups after 1 week up to 12 months.
Hinde 2020 Access date: April 2018	To summarize the literature and perform a meta-analysis on the mortality outcomes of patients with osteoporotic VCF treated with Vertebral augmentation compared with those	Osteoporotic VCFs	PV, KP, or both vs. CMT§ (aim was to compare vertebral augmentation with CMT)	Mortality	Meta-analysis of comparative cohort studies: 2 prospective, 14 retrospective	**PV/KP vs. CMT:** PV/KP associated with slightly lower mortality overall (7 studies, HR 0.78, 95%CI 0.66 to 0.92), at two years (5 studies, HR 0.70, 95% CI 0.69 to 0.71) and 5 years (3 studies HR 0.70, 95%CI 0.62 to 1,00) The extent to which confounding factors were controlled in studies and rational for

Assessment (year) Search dates	Purpose	Condition	Treatments vs. controls	Primary Outcomes	Evidence-base Used	Primary Conclusions
	in patients treated with CMT.					study selection for meta-analysis are unclear.
Sørensen 2019 Search dates: January 1, 2000 to January 3, 2018	To perform a systematic review evaluating the effectiveness and safety of vertebral augmentation for malignant VCFs.	Malignant VCFs	Studies evaluating patients treated with either PV or KP were included	Visual Analog Scale (VAS), Oswestry Disability Index (ODI), Karnofsky Performance Score (KPS)	2 RCTs**, 16 prospective studies, 44 retrospective studies, and 25 case series or reports‡	At the earliest follow-up (<4 weeks), pain improved from 7.48 to 3.00 with PV, and from 7.05 to 2.96 with KP. At the earliest follow-up (<4 weeks), ODI improved from 74.68 to 17.73 with PV, and from 66.02 to 34.73 with KP. At the earliest follow-up (<4 weeks), KPS improved from 66.99 to 80.28 across patients treated with either KP or PV. **Safety**: VP vs. KP Cement leakage: 37.9% (1157/2091) vs. 13.6% (206/1335) Across all patients treated with either VP or KP, there were only 43 cases of symptomatic complications, indicating that symptomatic complications are rare.

CI: confidence interval; CMT = conservative medical treatment; EQ-5D: EuroQol-5D; KP: percutaneous kyphoplasty; MCID: minimal clinically important difference; MD: mean difference; NR: not reported; OVCF: osteoporotic vertebral compression fracture; PV: percutaneous vertebroplasty, RCTs: randomized controlled trials; RMDQ/RDQ: Roland-Morris disability questionnaire, RR: Risk Ratio; SMD: standard mean difference; VAS: visual analog scale; VCS: vertebral compression fracture.

*Buchbinder 2018 defined a minimal clinically important difference of 1.5 points on a 10-point pain scale.

†The definition of a "clinically important" amount was defined in individual RCTs: improvement from baseline of >2.5 points or 30% on 0-10 scale or pain <4 out of 10 points.

‡Authors do not provide definitions for what they are considering a prospective/retrospective study and a case series, so it is not possible to distinguish comparative studies from non-comparative ones. Nevertheless, even if an included study was comparative, the authors did not use it as such.

§ Some studies included patients undergoing VP or KP alone, others included patients undergoing both procedures but analyzed these two procedures separately, and still others included both procedures but analyzed data under the umbrella of vertebral augmentation alone.

**One of the RCTs included in this SR would not meet the inclusion criteria for this review, as it is a comparison of different methods.

Appendix Table B2. Study characteristics and results of newly identified RCTs not included in Buchbinder 2018 SR

Author (Year)	Demographics	Results	Author's Conclusions	Comments
PV vs. Sham				
Firanescu 2019 (Safety specific publication for VERTOS IV trial)	N=180 Fracture type: osteoporotic vertebral compression *PV vs. sham* Age, mean: 74.7 vs. 76.9 years Female: 67% vs. 66% Median (IQR) number of days with back pain before procedure: 43 (29 to 52) vs. 36 (24 to 51) days Baseline VAS (0-10), mean (SD): 7.7 (1.4) vs. 7.9 (1.6) Fracture age: NR Number of levels treated: One: 61% (55/90) vs. 61% (53/86) Two: 26% (23/90) vs. 28% (24/86) Three 13% (12/90) vs. 11% (9/86) PV (n=91): PV using Polymethylmethacrylate with local anesthetics exclusively, with osteoporosis medication and pain medication if necessary Sham (n=89): Simulated PV without cement F/U: 1 day, 1, 3, 6, 12 months	Safety: PV vs. Sham Proportion of patients reporting new fractures at 12 months: • All cases: 16.6% (15/90) vs. 22.1% (19/86), RR 0.75 (95% CI 0.41 to 1.39) - Cases considered symptomatic with bone oedema on MRI: 40% (6/15) vs. 31% (6/19) Distribution of new OVCFs (n=31 vs. 28 fractures; data NR per patient): • Adjacent: 52% (16/31) vs. 50% (14/28), , RR 1.03 (95% CI 0.62 to 1.71) • Distant: 45% (14/31) vs. 46% (13/28), RR 0.97 (95% CI 0.56 to 1.70) • Between (sandwich): 3% (1/31) vs. 4% (1/28), RR 0.90 (95% CI 0.06 to 13.77) Proportion of PV treated vertebrae experiencing cement leakage (all were asymptomatic†): • Any leakage type: 91.3% (105/115 treated vertebrae) - Leakage type 1 (disc above): 20% - Leakage type 2 (disc below): 15% - Leakage type 3 (perivertebral soft tissue): 10% - Leakage type 4 (perivertebral veins): 39% - Leakage type 5 (pulmonary): 7% - Leakage type 6 (spinal canal): 8%	**Safety:** No statistically significant differences between groups of new vertebral fractures, risk of adjacent vs. distant vertebrae, or cement volume compared to cement leakage.	Authors report no conflict of interest Authors reports that the study was supported by Stryker (Grant No. S-I-013)

Author (Year)	Demographics	Results	Author's Conclusions	Comments
		Adverse Events (data NR by group) • Development of respiratory insufficiency due to COPD GOLD IV: 0.57% (1/176) • Self-correcting vasovagal reaction: 0.57% (1/176)		
KP vs. CMT				
Li 2017	N = 80 Fracture Type: Osteoporotic thoraco-lumbar compression fractures *KP vs. CMT* Age, mean (SD): 74.3 (7.0) vs. 74.4 (7.4) Pain duration, mean: NR Fracture age: NR (inclusion criteria included having a course of disease lasting 2 hours to 2 weeks) Number of levels treated: NR	<u>Pain: KP vs. CMT</u> VAS (0-10), mean (SD) • Baseline: 8.60 (0.46) vs. 8.43 (0.60), MD 0.17 (95% CI -0.07 to 0.41) • 3 days: 2.10 (0.28) vs. 8.32 (0.37), MD -6.22 (95% CI -6.37 to -6.04) • 1 week: 3.80 (0.35) vs. 7.20 (0.38), MD -3.40 (95% CI -3.56 to -3.24) • 1 month: 2.64 (0.22) vs. 3.10 (0.45), MD -0.46 (95% CI -0.62 to -0.30) • 3 months: 1.42 (0.34) vs. 2.38 (0.52), MD -0.96 (95% CI -1.16 to -0.76) • 6 months: 1.02 (0.24) vs. 1.53 (0.21), MD -0.51 (95% CI -0.61 to -0.41) <u>Function: KP vs. CMT:</u> ODI (0 to 100), mean (SD) Baseline: 42.3 (6.7) vs. 41.3 (6.2), MD 1.0 (95% CI -1.87 to 3.87) 3 days: 20.2 (5.4) vs. 36.5 (5.1), MD -16.30 (95% CI -18.64 to -13.96) 1 week: 18.5 (4.3) vs. 19.7 (3.4), MD -1.20 (95% CI -2.93 to 0.53) 1 month: 15.1 (3.6) vs. 18.7 (5.3), MD -3.60 (95% CI -5.62 to -1.58)	**Pain and Function**: As far as conservative treatment is concerned, the trauma is small, but the vertebral body could not get complete recovery and it may cause more complications. So, it is only suitable for elderly patients with mild compression symptoms or intolerable to surgery. In contrast, the KP treatment, with more immediate pain relief, greater height restoration in affected ver-tebras and better correction in kyphosis, is an effective alternative for treatment of OVCFs in the elderly.	Authors report no conflict of interest Authors do not report financial support information

Author (Year)	Demographics	Results	Author's Conclusions	Comments
		3 months: 14.2 (4.2) vs. 18.2 (5.0), MD -4.0 (95% CI -6.06 to -1.95)		
Liu 2019a	N = 116 Fracture Type: Multiple senile osteoporosis spinal *KP vs. CMT* Age, mean (SD): 65.34 (2.57) vs. 65.78 (2.81) Female: 67% vs. 50% Pain Duration, mean: NR Fracture Age: NR Number of levels treated: NR KP (n=58): Balloon KP using Omnipaque under continuous C-arm fluoroscopy, with local anesthesia in prone posture. CT (n=58): Patients in the control group were provided with conservative treatment, including analgesia using drugs, physical treatment, and fixation treatment, and maintained in bed for 3 months. F/U: NR ("post-treatment")‡	<u>Pain: KP vs. CMT</u> VAS Pain Intensity (0-10), mean (SD): • Baseline: 8.56 (0.39) vs. 8.58 (0.36), MD -0.02 (95% CI -0.16 to 0.12) • Post-treatment‡: 2.25 (0.21) vs. 4.54 (0.28), MD -2.29 (95% CI -2.38 to -2.20) <u>Function: KP vs. CMT:</u> Barthel Index (0-100), mean (SD): • Baseline: 89.76 (5.27) vs. 89.83 (4.37), MD -0.07 (95% CI -4.85 to 1.71) • Post-treatment‡: 24.34 (4.53) vs. 31.57 (4.25), MD -7.23 (95% CI -8.85 to -5.61) <u>(Safety): KP vs. CMT</u> Bone cement leakage resulting in complications: 1.72% (1/58) vs. 0% (0/58) Development of embolism: 0% (0/58) vs. 1.72 (1/58) Development of decubitus: 0% (0/58) vs. 6.9% (4/58) Complication due to infection: 0% (0/58) vs. 6.9% (4/58) Occurrence Rate of complication:	**Pain & Function:** No statistically significant differences between groups at baseline for pain and disability. There was a statistically significant difference between groups post-treatment for pain and function. **Occurrence of Complication (Safety):** Statistically significant difference between groups post-treatment.	Authors report no conflict of interest Authors report that no financial support or sponsorship were received

Author (Year)	Demographics	Results	Author's Conclusions	Comments
		1.72% vs 15.52%, p<0.05		
KP vs. PV				
Liu 2019b	N = 100 Fracture Type: Osteoporotic Spinal *KP vs. PV* Age, mean (SD): 73.23 (2.05) years (all patients) Female: 44% (all patients) Pain duration: NR Fracture age: NR Number of levels treated: NR KP (n=50): Balloon KP with developer using anesthesia under constant x-ray monitoring. PV (n=50): PV with PMMA using anesthesia under constant x-ray monitoring F/U: 1 month	<u>Pain: KP vs. PV</u> VAS Pain Intensity (0-10), mean (SD): • 1 month: 1.96 (0.32) vs. 1.98 (0.48), MD -0.02 (95% CI -0.18 to 0.14) <u>Function: KP vs. PV</u> ODI Disability (%), mean (SD): • 1 month: 29.97 (3.61) vs. 30.04 (2.67), MD -0.07 (95% CI -1.33 to 1.19)	**Pain & Function:** No statistically significant differences between groups on any pain outcomes on VAS or function on ODI. Suggests both can effectively relieve patient's pain and improves disability.	NR

CMT: conservative medical treatment; F/U: follow-up; KP: percutaneous kyphoplasty; KPS: Karnofsky performance status; MCID: minimal clinically important difference; MD: Mean Difference; MRI: magnetic resonance imaging; NS: not significant; NR: not reported; NRS: numerical rating score; ODI: Oswestry disability index; OVCF: osteoporotic vertebral compression fractures PMMA: Polymethyl methacrylate; PV: Percutaneous Vertebroplasty; RDQ: Roland-Morris disability index; SD: standard deviation; RR: Risk Ratio; SF-36 PCS: short form (36) physical component summary; VAS: visual analog scale

*Four patients were excluded post-randomization: 1 in PV group for presence of >3 fracture levels, 2 in sham group for diagnosis of multiple myeloma after randomization, and 1 in sham group for a missing intake form.

†Could not compare cement leakage with sham group since sham group did not receive cement.

‡Authors do not further specify when follow-up measures were completed.

APPENDIX C. RESULT FOR SECTION 4: SIGNAL UPDATE SUMMARY TABLES BY KEY QUESTION

Table C1. Vertebroplasty, Kyphoplasty, Sacroplasty Summary Table for Key Question 1.

Key Question 1. What is the evidence of efficacy and effectiveness of vertebroplasty, kyphoplasty, and sacroplasty?				
Conclusions from CER Executive Summary	**Conclusions from 2016 Signal update**	**New Sources of Evidence**	**New Findings-**	**AAI Conclusions 2020 Signal update**
<u>Vertebroplasty (PV) vs. sham surgery</u> There is low evidence from two RCTs, PV was no more effective than sham surgery in reducing pain or improving function or quality of life at one month and three months. Pain improved in both groups by 2.6-3.0 points at follow-up, RDQ scores improved by 3.7-5.3, and EQ-5D improved by 0.1-0.2 points.	**Efficacy**: • Short term (≤ 6months): Preliminary pooled analysis which includes the new RCT suggests an important change in the evidence for pain improvement success from no difference to difference favoring PV. (Criterion B1). • Short term: Pooled estimates for function do not provide a major change in the evidence (Criteria B1-4) Longer term (>6 months to 24 months) Updated analyses from the systematic review do not change the conclusions of the previous report (criteria A-1 or A3) nor provide major changes in the evidence (Criteria B1-4)	**Efficacy:** *Cochrane Systematic Review (SR): Buchbinder 2018 (Updates Buchbinder 2015; includes 2 new RCTs since 2016 report, 3 new since the original HTA report)* **Effectiveness** Not explored	**Efficacy**: • Pain "success" (improvement from baseline of >2.5 points or 30% on 0-10 scale or pain <4 out of 10 points): Analyses up to 12 months do not include new trials compared with the 2016 report which noted a shift from no statistical difference between groups in the original HTA to marginally significant (lower bound for 95% CIs ranged from 0.99 to 1.12) at 1, 3 and 6 months. New pooled analysis at 12 months (2 trials [1 new]) suggests that more PV patients experience clinically meaningful pain relief versus sham (66% vs. 50.9%, pooled RR 1.29, 95% CI 1.06 to 1.58) • Consistent with the 2016 signal update report, no clinically meaningful mean between-group differences* in outcome were observed for pain, RDMQ, QUALEFFO, EQ-5D at any time point in patients with osteoporotic fractures based on pooled analysis including new RCTs in the Buchbinder	• With regard to pain "success" the addition of 3 new RCTs since the prior report suggests a change in evidence from no difference to a difference favoring PV. (Criterion B1) • Updated analyses of mean differences between groups in the new systematic review overall do not change the conclusions of the previous report (criteria A-1 or A3) nor provide major changes in the evidence (Criteria B1-4). • Overall strength of evidence (SOE) may be impacted

Key Question 1. What is the evidence of efficacy and effectiveness of vertebroplasty, kyphoplasty, and sacroplasty?				
Conclusions from CER Executive Summary	**Conclusions from 2016 Signal update**	**New Sources of Evidence**	**New Findings-**	**AAI Conclusions 2020 Signal update**
			Cochrane review up to 24 months. Statistical significance for pooled estimates was only reached at 1 month for VAS pain (5 trials [2 new since 2016], MD –0.73 95% CI –1.18 to –0.28) and RMDQ (4 trials [1 new], MD –1.5, 95% CI –2.61 to –0.38). **Effectiveness:** Not explored	
<u>Vertebroplasty (PV) vs. conservative treatment (CMT); unblinded</u> • **Efficacy:** There is low evidence: • In a large RCT comparing PV with conservative treatment, PV was more effective than conservative treatment in reducing self-reported pain intensity for follow-up points of up to one year, with improvements of 6.6 points and 3.7 points respectively. • In this large RCT, improvement in RDQ scores was greater for PV patients than for CMT patients by 2-3 points over a year. PV patients also improved more than CMT patients on the QualEffo, but scores for the two groups were similar at 12 months.	**Efficacy**: Findings from systematic reviews including new RCTs do not change the conclusions from the previous report (criteria A-1 or A3), nor provide major changes in the evidence (criteria B1-B4). Across two SRs, PV improved pain and disability and EQ-5D across time frames but there was inconsistency in statistical significance across time frames. Differences in QAULEFFO were not statistically significant.	*Cochrane Systematic Review (SR): Buchbinder 2018 (Updates Buchbinder 2015 with 2 new RCTs. A total of 5 new RCTs since the 2010 HTA)*	**Efficacy:** • PV was associated with improved mean VAS pain and function (RMDQ or ODI) at all time frames from 2 weeks to 24 months based on pooled estimates versus CMT; potentially clinically important differences* were seen for VAS pain at 1 month (3 trials, MD –2.06, 95% CI –3.35 to –0.76) and for RMDQ at 1 to 2 weeks (5 trials, SMD –2.06, 95% CI –3.28 to –0.83), 3 months (4 trials, SMD –2.76, 95% CI –4.65 to –0.87), and 24 months (1 trial SMD –5.65, 95% CI –6.67 to –4.63). • Differences between groups for QAULEFFO were not	• Pooled findings based on inclusion of 5 new RCTs, published after the original HTA suggests a change in evidence from no consistent statistically significant difference to a difference favoring PV that may be clinically meaningful when compared with CMT. (Criterion B1) • Overall strength of evidence (SOE) may be impacted

Key Question 1. What is the evidence of efficacy and effectiveness of vertebroplasty, kyphoplasty, and sacroplasty?				
Conclusions from CER Executive Summary	**Conclusions from 2016 Signal update**	**New Sources of Evidence**	**New Findings-**	**AAI Conclusions 2020 Signal update**
• In two small RCTs, PV and CMT patients showed comparable improvement in pain, with inconsistent findings for functional outcomes. • **Effectiveness:** There is low evidence • In four cohort studies (2 prospective, 2 retrospective): ○ PV was more effective than CMT in reducing pain (from 7.5-9 to 0.7-3.5) up to 6 months, but pain levels were comparable for the two groups after one year. ○ For a very limited set of functional outcomes, PV led to earlier improvements than CMT, followed by equivalent levels of functioning after 6 months to a year.			statistically significant at any time frame. • Differences in EQ-5D were potentially clinically important and statistically significant at 1 to 2 weeks (MD 0.08, 95% CI 0.00 to 0.15) and 1 month (MD 0.09, 95% CI 0.01 to 0.16) based on 1 trial and at 3 months across 2 trials (pooled MD 0.10, 95% CI 0.00 to 0.20); statistical significance was not reached at 6 months (1 trial) or 12 months (2 trials). **Effectiveness:** Not explored	
<u>Kyphoplasty (KP) vs. conservative treatment (CMT); unblinded</u> • **Efficacy**: • There is low evidence from one RCT • KP was more effective than CMT by 0.9-2.2 points in reducing pain intensity for follow-up points up to one year. • Pain was reduced more rapidly in KP patients, and group	**Efficacy**: Analyses from the systematic reviews which include updated data from RCTs do not change the conclusions from the previous report (criteria A-1 or A3), nor provide major changes in the evidence (criteria B1-B4).	***RCTs (Osteoporotic fractures)*** *Li 2017* *Liu 2019a* ***Systematic review*** *(pathologic fractures)* *Sorenson, 2019*	**Efficacy:** Osteoporotic fractures • Two new poor quality RCTs have been published since the original HTA and 2016 signal update. Neither provides data on longer term outcomes. • Preliminary pooled estimates combining data from the RCT from the prior HTA with the new Li 2017 RCT suggest that KP is associated with improved VAS pain at 3 months (MD –1.22,	• While 2 additional RCTs have been published in patients with osteoporotic fractures, both are poor quality and not considered pivotal and do not change the conclusions from the previous report (criteria A-1 or A3), nor provide major changes in the evidence (criteria B1-B4).

Key Question 1. What is the evidence of efficacy and effectiveness of vertebroplasty, kyphoplasty, and sacroplasty?				
Conclusions from CER Executive Summary	**Conclusions from 2016 Signal update**	**New Sources of Evidence**	**New Findings-**	**AAI Conclusions 2020 Signal update**
differences were diminished by 12 months. • KP was more effective than CMT in improving functional outcomes (EQ-5D, RDQ, SF-36) over one year, but group differences were diminished at 12 months. • **Effectiveness:** There is very low evidence from two cohort studies (1 prospective and 1 retrospective): • KP reduced pain more than CMT for periods up to 3 years. • KP improved a limited set of functional outcomes more than CMT			95% CI –1.82 to –0.61) but not at 1 month (MD 1.19, 95% CI –2.66 to 0.28) or 6 months (MD –1.03, 95% CI –2.11 to 0.06). Differences are not likely to be clinically meaningful. Li 2017 reports a clinically important improvement in pain at 3 days (MD –6.22, 95% CI –6.36 to –6.08). Liu 2019 also reports lower VAS pain with KP versus CMT (MD –2.29 95% CI –2.38 to –2.2) post-treatment (timing NR). • Both new trials report an association between KP and improved function compared with CMT. Preliminary pooled estimates combining data from the RCT from the prior HTA with the new Li 2017 RCT suggest that KP is associated with improved function (ODI or RMDQ) at 1 month (SMD –0,72, 95% CI –0.93 to –0.51) and 3 months (SMD –0.65, 95% CI –0.85 to –0.43) vs. CMT. The differences may be clinically important. • Barthel Index (Liu 2019a) at an undefined time posttreatment (MD -7.23; 95% CI -8.85 to -5.61) was also significantly improved.	• For malignant fractures, additional evidence in the systematic review is primarily from observational studies. This does not change the conclusions from the previous report (criteria A-1 or A3), nor provide major changes in the evidence (criteria B1-B4).

Key Question 1. What is the evidence of efficacy and effectiveness of vertebroplasty, kyphoplasty, and sacroplasty?				
Conclusions from CER Executive Summary	**Conclusions from 2016 Signal update**	**New Sources of Evidence**	**New Findings-**	**AAI Conclusions 2020 Signal update**
			Pathological† fractures • One SR of patients with fractures due to malignancy, includes an RCT, prospective and retrospective comparative studies and case series. • SR includes the RCT identified in the 2016 report (KP vs. CMT) plus data from 85 observational studies of KP and PV in 3456 patients with pathological VF. Data are presented only for PV and KP with no comparison to other treatments. • Across studies, compared with baseline values, authors report improvements in VAS pain, ODI and KPS that are likely clinically important. Improvements were sustained past 12 months. Comparative data are not reported. (See abstraction.) **Effectiveness:** Not explored	
<u>Vertebroplasty (VP) vs. kyphoplasty (KP)</u> • **Efficacy**: There is very low evidence from one poor-quality RCT that back pain scores improved equally (from 8.0 to 2.3-2.6) for PV and KP patients over 6 months • **Effectiveness:** There is low evidence from 12 cohort studies	**Efficacy:** Updated analyses from the systematic review including new RCTs do not change the conclusions from the previous report (criteria A-1 or A3), nor provide major changes in the evidence (criteria B1-B4).	***Cochrane Systematic Review (SR):*** *Buchbinder 2018 (Updates Buchbinder 2015. A total of 5 new RCTs and updated finding from 1 RCT*	**Efficacy:** • Consistent with the prior HTA and 2016 update, there was no difference between VP and KP for pain, function (ODI) or EQ-5D at any time point in one high quality SR. (see data abstraction)	**Efficacy:** • Updated analyses in the SR including new RCTs together with the additional poor-quality trial do not change the conclusions from the previous report (criteria A-1 or A3), nor provide

Key Question 1. What is the evidence of efficacy and effectiveness of vertebroplasty, kyphoplasty, and sacroplasty?				
Conclusions from CER Executive Summary	**Conclusions from 2016 Signal update**	**New Sources of Evidence**	**New Findings-**	**AAI Conclusions 2020 Signal update**
(6 prospective and 6 retrospective) that: • PV and KP led to comparable pain reduction (from 7.2-8.8 at baseline to 0.6-4.6) at follow-up periods up to 2 years in 8 of 10 studies. • PV and KP demonstrated comparable improvements (from 30.8-77 to 4.8-56) in the ODI at follow-up times up to 2 years in 4 of 5 studies		*since the 2010 HTA are included)* ***RCT**: Liu 2019b (not in SR)*	• The Liu 2019b trial also reported no differences between VP and KP in pain or ODI function at 1 month **Effectiveness:** Not explored	major changes in the evidence (criteria B1-B4). • Overall SOE could be impacted.
<u>Vertebroplasty (VP) vs. facet joint injection</u> No studies identified	**Not applicable**	***Cochrane Systematic Review (SR):*** *Buchbinder 2018; Additional RCT with new comparator*	**Efficacy:** • The SR includes 1 RCT (Wang 2016) which compares VP vs. facet joint injection. While a statistically significant and potentially clinically important improvement in VAS pain was associated with VP vs. injection at 1 to 2 weeks (MD –1.61, 95% CI –1.84 to –1.38) this did not persist for time frames up to 12 months. • Similarly, improved function (RMDQ) was seen at 1 to 2 weeks (MD –3.42, 95% CI –3.72 to –3.12) and may be clinically meaningful but did not persist to later time frames. • No difference between groups was seen for SF-36 total score	• Facet joint injection represents a new comparator not contained in the original HTA. However, the findings from a single RCT of this comparison do not meet the criteria that would trigger an updated report. (Criteria A-3, B1-4).

Key Question 1. What is the evidence of efficacy and effectiveness of vertebroplasty, kyphoplasty, and sacroplasty?				
Conclusions from CER Executive Summary	**Conclusions from 2016 Signal update**	**New Sources of Evidence**	**New Findings-**	**AAI Conclusions 2020 Signal update**
			Effectiveness: Not explored	
<u>Sacroplasty</u> No comparative studies identified. There is very low evidence across four case series that suggests improvement in pain following sacroplasty.	**Efficacy:** No new comparative studies identified, No new evidence **Effectiveness:** Not explored	**Efficacy:** No systematic reviews of comparative studies identified. No RCTs identified. **Effectiveness:** Not explored	**Efficacy:** No RCTs or systematic reviews of RCTS were identified to evaluate efficacy. Two SRs of observational studies (Chandra, Mahmood) reported only single arm results (not comparative) so were excluded at full text. Overall, they reported improved pain and function relative to baseline values with use of sacroplasty. The reviews did cite 2 comparative observational studies (Frey 2017, Yang 2018) which appear to be of poor quality that might meet inclusion criteria if a re-review is done.	• No RCTs identified. Conclusions from the previous report (criteria A-1 or A3), do not change. There are no major changes in the evidence for efficacy (criteria B1-B4).

CI = confidence interval; CMT = conservative medical management; EQ-5D = European quality of life questionnaire five dimensions; HTA = health technology assessment; KP = percutaneous kyphoplasty; KPS = Karnofsky Performance Score; MD = mean difference; NR = not reported; ODI = Oswestry Disability Index; PV = percutaneous vertebroplasty; QUALEFFO = Quality of Life Questionnaire of the European Foundation for Osteoporosis; RCT = randomized control trial; RMDQ = Roland Morris Disability Questionnaire; RR = risk ratio; SMD = standardized mean difference; SOE = summary of evidence; SR = systematic review; VAS = visual analog scale; VF = vertebral fracture

*Defined by Buchbinder as 1.5 points on a 10-point pain scale; two to three points on the zero- to 23-point RMDQ, 10 points on the zero to 100 QUALEFFO scale, 0.074 points on the EQ-5D.

†Pathologic fractures may include multiple myeloma, hemangioma, or metastases.

Table C2. Vertebroplasty, Kyphoplasty, Sacroplasty Summary Table for Key Question 2.

Key Question 2: What is the evidence of the safety of vertebroplasty, kyphoplasty or sacroplasty?				
Conclusions from CER Executive Summary	**Conclusions from 2016 Signal update**	**New Sources of Evidence**	**New Findings**	**AAI Conclusions 2020 Signal update**
Vertebroplasty (VP) and Kyphoplasty (KP) There is low evidence for the following outcomes: • New fractures: ○ In comparative studies, the rate of new fractures at any location following PV, KP, or CMT was up to 25% at 6 months post-surgery, and up to 30% at 12 months, with no consistent pattern across studies in different rates for PV, KP, and CMT. ○ In cohort studies, from 22% to 66% of new fractures occurred in adjacent vertebrae, however, these rates are based on very small numbers. A systematic review concluded that the proportion of new fractures that were adjacent was higher for KP (75%) than for PV (52%). ○ Systematic reviews of case series report slightly higher rates of new fractures at any	• New RCTs included in systematic reviews do not change the conclusions from the previous report (criteria Criterion A-2).	***Cochrane Systematic Review (SR):*** *Buchbinder 2018* ***Systematic review****: Hinde 2020* ***Systematic review*** *Sørensen 2019 (malignant fractures)* ***RCTS****: VP vs. sham Safety update (VERTOS IV trial): Firanescu 2019* *KP vs. CMT Liu 2019a* *PV vs. facet injection*	• New fractures: ○ Buchbinder 2018: VP vs. Sham or CMT • No differences between treatment groups in either new clinical fractures (6 RCTs, RR 1.29, 95% CI 0.46 to 3.62) or radiographic fractures (8 RCTs RR 1.14, 95% CI 0.71 to 1.84) were seen but there was substantial statistical heterogeneity (67% to 70%). ○ Buchbinder 2018: VP vs. KP • Clinical fractures (no new evidence) • No differences between treatments in 2 trials at 12 months (RR 0.81, 95% CI 0.21 to 3.16) in radiographic fractures ○ Buchbinder 2018: VP vs. facet injection • No difference in radiographic fractures (RR 1.25, 95% CI 0.59 to 2.67) (Wang 2016) ○ Firanescu 2019: VP vs. sham • Any fracture (RR 0.75, 95% CI 0.41 to 1.39); 6 in each group were symptomatic and had bone edema on MRI; frequency of adjacent fractures was similar between groups. • Serious adverse events ○ Buchbinder 2018 (events judged to be due to procedure, e.g. infection complications from cement leakage) • PV vs. sham or CMT: No differences (5 trials, RR 0.61, 95% CI 0.33 to 1.10) • PV vs. KP: 12 months, 1 trial (n=100), no difference, 0 vs. 2 events. ○ Firanescu 2019, PV vs. sham: respiratory insufficiency 0.57% (1/176) (group NR) ○ Liu 2019a: KP vs. CMT	• New RCTs included in systematic reviews do not change the conclusions from the previous report (criteria Criterion A-2) for new fractures and serious adverse events as reported. • No new RCT data are reported related to mortality. A new SR of observational studies suggests that mortality may be lower in those receiving PV or KP vs. CMT in contrast to the findings of a SR identified in the 2016 report. Differences should be explored in greater depth and this section of the report could be updated (Criteria A-2, B-1) • Given potential limitations of RCT data for rare and long-term harms, evaluation of observational data on safety could be considered for an update review.

Key Question 2: What is the evidence of the safety of vertebroplasty, kyphoplasty or sacroplasty?				
Conclusions from CER Executive Summary	**Conclusions from 2016 Signal update**	**New Sources of Evidence**	**New Findings**	**AAI Conclusions 2020 Signal update**
location for PV (16-21%) than for KP (7-17%). • Cement leakage ○ Rates of asymptomatic cement leakage are up to 80% for vertebroplasty and 50% for kyphoplasty. ○ Comparative studies and systematic reviews (consisting largely of case series) suggest that cement leakage is greater in PV than in KP; however, symptomatic leaks are rare (up to 1.6% in PV and 0.3% in KP; data from reviews of case series) • Pulmonary cement embolism (PCE) ○ One RCT reported a PCE rate for PV of 26%, with all cases asymptomatic ○ Systematic reviews of case series report pooled PCE rates from 0.1% to 1.7%, with insufficient information to compare rates for PV and KP. • Mortality: Data from systematic reviews primarily of case series		*Wang 2016 (in Buchbinder)*	• Overall complications (to include cement leakage, venous embolism, decubitus, and infection: 1.72% vs. 15.52% ($p<0.05$) • Embolism: 0% vs. 6.9% • Infection: 0% vs. 6.9% • Cement Leakage overall continues to be common; new evidence on complications related to leakage is limited: ○ Firanescu 2019 PV vs. sham: Leakage in 91.3%; All were asymptomatic. ○ Liu 2019a: Leakage resulting in complications, KP (1.72%) vs. CMT 0% ○ Sorensen SR (observational studies): VP vs. KP Cement leakage: 37.9% vs. 13.6% • Mortality • Buchbinder 2018: Not reported • Hinde (poor quality): Meta-analysis of observational/administrative database studies comparing either PV or KP with CMT published between 2006 and 2018; ○ PV/KP associated with slightly lower mortality overall (7 studies, HR 0.78, 95% CI 0.66 to 0.92), at 2 years (5 studies, HR 0.70, 95% CI 0.69 to 0.71) and 5 years (3 studies, HR 0.70, 95% CI 0.62 to 1.00) vs. CMT. The extent to which selection bias related to uncontrolled confounding and other factors may impact results is unclear. Rationale for selection for meta-analysis was not clearly reported. A 2015 SR of RCTs described in the 2016 update report found no difference between	• Overall SOE could change for some outcomes.

Key Question 2: What is the evidence of the safety of vertebroplasty, kyphoplasty or sacroplasty?				
Conclusions from CER Executive Summary	**Conclusions from 2016 Signal update**	**New Sources of Evidence**	**New Findings**	**AAI Conclusions 2020 Signal update**
○ Rates in prospective studies of 2.1% (22/1051) for PV and 0.6% (24/5629) for retrospective studies. ○ Overall mortality for kyphoplasty ranging from 2.3% (13/588) to 3.2 % (25/522) from 2 different reviews ○ Perioperative mortality: 0.01% (1/406).			augmentation procedures and control groups. • Other adverse events: o Buchbinder: PV vs. sham or CMT • No between-group differences o Buchbinder: PV vs. KP • No difference between groups in one newer study	
<u>Sacroplasty</u> • There is very low evidence across four case series that the rate of cement leakage was 20.5% (7/34 patients)	No systematic reviews or RCTs identified	No systematic reviews or RCTs identified	No new evidence	No new evidence

CI = confidence interval; CMT = conservative medical management; HTA = health technology assessment; KP = percutaneous kyphoplasty; MRI = magnetic resonance imaging; NR = not reported; PV = percutaneous vertebroplasty; RCT = randomized control trial; RR = risk ratio; SOE = summary of evidence; SR = systematic review; VF = vertebral fracture

Table C3. Vertebroplasty, Kyphoplasty, Sacroplasty Summary Table for Key Questions 3 and 4.

Key Question 3: What is the evidence that vertebroplasty, kyphoplasty or sacroplasty has differential efficacy or safety in subpopulations?				
Conclusions from CER Executive Summary	**New Sources of Evidence**	**New Sources of Evidence**	**New Findings**	**AAI Conclusions 2020 Signal update**
<u>Vertebroplasty (VP) vs. sham surgery or conservative treatment (CMT)</u> There is very low evidence regarding the following: • Fracture age ○ No studies were designed to directly compare efficacy or safety outcomes between patients with acute, subacute, and/or chronic fractures. ○ Two RCTs reported that improvements in pain and functional outcomes were not significantly different for patients with acute and chronic fractures; however, the studies may not have had adequate power for these post-hoc analyses. ○ One RCT of PV vs. CMT in patients with acute fractures reported greater improvement in pain and function for PV patients, but evidence for differential efficacy cannot be derived since there was no direct comparison with more chronic fractures in the same underlying population • Osteoporotic versus malignant fractures ○ Two retrospective cohort studies in patients with malignancy fractures cannot provide information for differential	Findings from the systematic reviews and new RCTs do not change the conclusions from the previous report (criteria A-1 or A3), nor provide major changes in the evidence (criteria B1-B4)	***Cochrane Systematic Review (SR):*** *Buchbinder 2018;*	• Buchbinder 2018 evaluated potential for heterogeneity of treatment effect (i.e. interaction) by fracture age (acute vs. subacute) for pain and disability at 1 to 2 weeks and 1 month and EQ-5D QOL at 1 month (data not abstracted). ○ While all tests for interaction for all outcomes at all time frames were not statistically significant, there was substantial variability in how studies defined "acute" and "subacute" and it is unclear that there was sufficient statistical power to detect such interaction. • Buchbinder 2018 evaluated the impact of control type on magnitude of pain and disability improvement at 1 to 2 weeks, 1 month and 3 months (data not abstracted). ○ Studies comparing PV or KP with sham consistently had smaller effect sizes that were either not statistically significant or were marginally significant and may possibly not be clinically important versus studies comparing	Findings from the systematic review do not change the conclusions from the previous report (criteria A-1 or A3), nor provide major changes in the evidence (criteria B1-B4) regarding differential efficacy.

efficacy based on fracture etiology.			augmentation to CMT for pain and function. ○ There was substantially more heterogeneity across studies comparing PV or KP with CMT for all outcomes.	
Kyphoplasty (KP) vs. conservative treatment (CMT) Very low evidence: No comparative studies were identified that assessed differential efficacy or safety according to patient, provider, or payer factors.	New RCT (pathologic fractures) does not change the conclusions from the previous report (criteria A-1 or A3), nor provide major changes in the evidence (criteria B1-B4).	***Systematic review**; patients with malignancy-related fractures; Sorenson 2019*	*Special population: pathologic fractures* *RESULTS ARE SUMMARIZED UNDER KQ 1 and KQ2*	See KQ 1 and 2
Vertebroplasty (VP) vs. kyphoplasty (KP) Very low evidence: • No comparative studies were identified that assessed differential efficacy or safety issues • Two retrospective cohort studies compared PV with KP among patients with fractures due to malignancy; one study reported comparable outcomes for PV and KP, and the other reported that KP led to more improvement in pain than PV over one year	No new evidence	No new evidence	No new evidence	No new evidence
Sacroplasty • Very low evidence: No comparative studies were identified	No new evidence.	No new evidence	No new evidence	No New evidence
Key Question 4: What are the cost implications and cost effectiveness of vertebroplasty, kyphoplasty and sacroplasty?				
Conclusions from CER Executive Summary	**New Sources of Evidence**	**New Sources of Evidence**	**New Findings**	**AAI Conclusions 2020 Signal update**

Vertebroplasty (PV) vs. sham surgery or conservative treatment (CMT) Very low Evidence: • One RCT reported that PV was associated with significant increases in cost and Quality Adjusted Life Years (QALY) at one month, but that these increases were no longer statistically significant by one year. • One retrospective cohort study reported that cost per patient per one-point reduction in pain rating (0-10 scale) was not significantly different for PV patients and CMT patients	New cost-utility study does not change the conclusions from the previous report (criteria A-1 or A-3), nor provide major changes in the evidence (criteria B-1).	No new evidence	No new evidence	No new evidence since 2016 signal update. Data identified in the 2016 report would update this section of the HTA. However, the findings from these studies do not meet the criteria that would trigger an updated report. (Criteria B1-4)
Kyphoplasty (KP) vs. conservative treatment (CMT) Very low evidence • Cost data from one RCT showed that KP was associated with increased cost and increased QALY compared with CMT.	New cost-utility studies do not change the conclusions from the previous report (criteria A-1 or A-3), nor provide major changes in the evidence (criteria B-1).	No new evidence	No new evidence	
Cancer-related vertebral compression fractures • **Vertebroplasty (PV) vs. non-surgical management** • **Kyphoplasty (KP) vs. non-surgical management** **No evidence in 2010 report**	New economic study does not change the conclusions from the previous report (criteria A-1 or A-3), nor provide major changes in the evidence (criteria B-1).	No new evidence	No new evidence	
Vertebroplasty (VP) vs. kyphoplasty (KP) No Evidence	No new evidence	No new evidence	No new evidence	No new evidence
Sacroplasty No Evidence	No new evidence	No new evidence	No new evidence	No new evidence

CMT = conservative medical management; EQ-5D = European quality of life questionnaire five dimensions; KP = percutaneous kyphoplasty; KQ = key question; NR = not reported; PV = percutaneous vertebroplasty; QALY = Quality adjusted life years; QOL = quality of life; RCT = randomized control trial; SR = systematic review; VF = vertebral fracture

APPENDIX D. PUBLICATIONS EXCLUDED AT FULL TEXT REVIEW

Appendix Table D1: List of references excluded at full text with reasons

Reference	Reason for Exclusion
Systematic Reviews	
1. Astur N, Avanzi O. Balloon Kyphoplasty in the Treatment of Neoplastic Spine Lesions: A Systematic Review. Global Spine J 2019;9:348-56.	Does not include any newly identified publications since the 2016 signal update.
2. Chandra V, Wajswol E, Shukla P, Contractor S, Kumar A. Safety and Efficacy of Sacroplasty for Sacral Fractures: A Systematic Review and Meta-Analysis. J Vasc Interv Radiol 2019;30:1845-54.	Does not include RCTs; SR of single arm data. Not the most up to date systematic review identified (i.e. did not include all relevant studies published to date).
3. Chen C, Shen X, Wang J, Zhang Z, Li Y, Chen H. Comparing pain reduction following kyphoplasty and vertebroplasty : A meta-analysis of randomized and non-randomized controlled trials. Orthopade 2017;46:855-63.	Not the most up to date systematic review identified (i.e. did not include all relevant RCTs published to date).
4. Fan B, Wei Z, Zhou X, et al. Does vertebral augmentation lead to an increasing incidence of adjacent vertebral failure? A systematic review and meta-analysis. Int J Surg 2016;36:369-76.	Due to the number of SRs identified by the signal search, only SRs published in 2017 and beyond were pulled for full text review.
5. Li H-M, Zhang R-J, Gao H, et al. New vertebral fractures after osteoporotic vertebral compression fracture between balloon kyphoplasty and nonsurgical treatment PRISMA. Medicine (Baltimore) 2018;97:e12666-e.	Includes a combination of RCTs and observational cohorts. Includes several studies that would not meet our inclusion criteria.
6. Mahmood B, Pasternack J, Razi A, Saleh A. Safety and efficacy of percutaneous sacroplasty for treatment of sacral insufficiency fractures: a systematic review. J Spine Surg 2019;5:365-71.	Does not include RCTs. No quantitative data of interest to report.*
7. Parreira PCS, Maher CG, Megale RZ, March L, Ferreira ML. An overview of clinical guidelines for the management of vertebral compression fracture: a systematic review. Spine J 2017;17:1932-8.	SR of clinical practice guidelines. References were checked.
8. Piazzolla A, Bizzoca D, Solarino G, Moretti L, Moretti B. Vertebral fragility fractures: clinical and radiological results of augmentation and fixation-a systematic review of randomized controlled clinical trials. Aging Clin Exp Res 2019:10.1007/s40520-019-01289-1.	Not the most up to date systematic review identified (i.e. did not include all relevant RCTs published to date). Includes many of the same RCTs as Buchbinder 2018 SR, with similar conclusions.
9. Pourtaheri S, Luo W, Cui C, Garfin S. Vertebral Augmentation is Superior to Nonoperative Care at Reducing Lower Back Pain for Symptomatic Osteoporotic Compression Fractures: A Meta-Analysis. Clin Spine Surg 2018;31:339-44.	Includes a combination of RCTs and observational cohorts. Not the most up to date systematic review identified (i.e. did not include all relevant RCTs published to date).

Reference	Reason for Exclusion
10. Qi L, Li C, Wang N, et al. Efficacy of percutaneous vertebroplasty treatment of spinal tumors: A meta-analysis. Medicine (Baltimore) 2018;97:e9575-e.	Search dates of SR too early (December 31, 2013 to January 1, 2015)
11. Rodriguez AJ, Fink HA, Mirigian L, et al. Pain, Quality of Life, and Safety Outcomes of Kyphoplasty for Vertebral Compression Fractures: Report of a Task Force of the American Society for Bone and Mineral Research. J Bone Miner Res 2017;32:1935-44.	Not the most up to date systematic review identified (i.e. did not include all relevant RCTs published to date). Includes studies that would not meet our inclusion criteria.
12. Sadeghi-Naini M, Aarabi S, Shokraneh F, Janani L, Vaccaro AR, Rahimi-Movaghar V. Vertebroplasty and Kyphoplasty for Metastatic Spinal Lesions: A Systematic Review. Clin Spine Surg 2018;31:203-10.	Does not include any newly identified publications since the 2016 signal update.
13. Wang B, Zhao C-P, Song L-X, Zhu L. Balloon kyphoplasty versus percutaneous vertebroplasty for osteoporotic vertebral compression fracture: a meta-analysis and systematic review. J Orthop Surg Res 2018;13:264-.	Includes a combination of RCTs and observational cohorts.
14. Xie L, Zhao Z-G, Zhang S-J, Hu Y-B. Percutaneous vertebroplasty versus conservative treatment for osteoporotic vertebral compression fractures: An updated meta-analysis of prospective randomized controlled trials. Int J Surg 2017;47:25-32.	Includes a combination of RCTs and observational cohorts.
15. Zhan Y, Jiang J, Liao H, Tan H, Yang K. Risk Factors for Cement Leakage After Vertebroplasty or Kyphoplasty: A Meta-Analysis of Published Evidence. World Neurosurg 2017;101:633-42.	Study of prognostic factors leading to cement leakage.
16. Zhang H, Xu C, Zhang T, Gao Z, Zhang T. Does Percutaneous Vertebroplasty or Balloon Kyphoplasty for Osteoporotic Vertebral Compression Fractures Increase the Incidence of New Vertebral Fractures? A Meta-Analysis. Pain Physician 2017;20:E13-E28.	Includes a combination of RCTs and observational cohorts.
17. Zhang Y, Shi L, Tang P, Zhang L. Comparison of the Efficacy Between Two Micro-Operative Therapies of Old Patients With Osteoporotic Vertebral Compression Fracture: A Network Meta-Analysis. J Cell Biochem 2017;118:3205-12.	This is a network meta-analysis. When possible, systematic reviews are preferred to network meta-analyses, as they provide a more direct comparison.
18. Zhao D-H, Chen K, Zhu J, Yang X, Dong F, Wang W-B. Postoperative Functional Evaluation of Percutaneous Vertebroplasty Compared With Percutaneous Kyphoplasty for Vertebral Compression Fractures. Am J Ther 2016;23:e1381-e90.	Due to the number of SRs identified by the signal search, only SRs published in 2017 and beyond were pulled for full text review.
19. Zhao G, Liu X, Li F. Balloon kyphoplasty versus percutaneous vertebroplasty for treatment of osteoporotic vertebral compression fractures (OVCFs). Osteoporos Int 2016;27:2823-34.	Due to the number of SRs identified by the signal search, only SRs published in 2017 and beyond were pulled for full text review.
20. Zhao S, Xu C-Y, Zhu A-R, et al. Comparison of the efficacy and safety of 3 treatments for patients with osteoporotic vertebral compression fractures: A network meta-analysis. Medicine (Baltimore) 2017;96:e7328-e.	This is a network meta-analysis. When possible, systematic reviews are preferred to network meta-analyses, as they provide a more direct comparison.
21. Zhu RS, Kan SL, Ning GZ, et al. Which is the best treatment of osteoporotic vertebral compression fractures: balloon kyphoplasty,	This is a network meta-analysis. When possible, systematic reviews

Reference	Reason for Exclusion
percutaneous vertebroplasty, or non-surgical treatment? A Bayesian network meta-analysis. Osteoporos Int 2019;30:287-98.	are preferred to network meta-analyses, as they provide a more direct comparison.
22. Zhu Y, Cheng J, Yin J, Zhang Z, Liu C, Hao D. Therapeutic effect of kyphoplasty and balloon vertebroplasty on osteoporotic vertebral compression fracture: A systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore) 2019;98:e17810-e.	Not the most up to date systematic review identified (i.e. did not include all relevant RCTs published to date).
23. Zuo X-H, Zhu X-P, Bao H-G, et al. Network meta-analysis of percutaneous vertebroplasty, percutaneous kyphoplasty, nerve block, and conservative treatment for nonsurgery options of acute/subacute and chronic osteoporotic vertebral compression fractures (OVCFs) in short-term and long-term effects. Medicine (Baltimore) 2018;97:e11544-e.	This is a network meta-analysis. When possible, systematic reviews are preferred to network meta-analyses, as they provide a more direct comparison.
Studies	
24. Firanescu CE, de Vries J, Lodder P, et al. Vertebroplasty versus sham procedure for painful acute osteoporotic vertebral compression fractures (VERTOS IV): randomised sham controlled clinical trial. BMJ 2018;361:k1551-k.	Included in Buchbinder 2018 SR.
25. Wang B, Guo H, Yuan L, Huang D, Zhang H, Hao D. A prospective randomized controlled study comparing the pain relief in patients with osteoporotic vertebral compression fractures with the use of vertebroplasty or facet blocking. Eur Spine J 2016;25:3486-94.	Included in Buchbinder 2018 SR.
26. Leali PT, Solla F, Maestretti G, Balsano M, Doria C. Safety and efficacy of vertebroplasty in the treatment of osteoporotic vertebral compression fractures: a prospective multicenter international randomized controlled study. Clinical Cases in Mineral and Bone Metabolism 2016;13:234.	Included in Buchbinder 2018 SR.
27. Sun K, Liu Y, Peng H, et al. A comparative study of high-viscosity cement percutaneous vertebroplasty vs. low-viscosity cement percutaneous kyphoplasty for treatment of osteoporotic vertebral compression fractures. Journal of Huazhong University of Science and Technology [Medical Sciences] 2016;36:389-94.	Included in Buchbinder 2018 SR.
28. Hansen EJ, Simony A, Carreon L, Rousing R, Tropp H, Anderson MO. Vertebroplasty vs. SHAM for Treating Osteoporotic Vertebral Compression Fractures: A Double Blind RCT. Integrative Journal of Orthopaedics and Traumatology Volume 2019;2:1-6.	Included in Buchbinder 2018 SR.
29. Wang B, Guo H, Yuan L, Huang D, Zhang H, Hao D. A prospective randomized controlled study comparing the pain relief in patients with osteoporotic vertebral compression fractures with the use of vertebroplasty or facet blocking. Eur Spine J 2016;25:3486-94.	Included in Buchbinder 2018 SR.
30. Andresen R, Radmer S, Andresen JR, Schober HC. Comparison of the 18-month outcome after the treatment of osteoporotic insufficiency fractures by means of balloon sacroplasty (BSP) and radiofrequency sacroplasty (RFS) in comparison: a prospective randomised study. Eur Spine J 2017;26:3235-40.	Comparison of techniques.
31. Andresen R, Radmer S, Andresen JR, Wollny M, Nissen U, Schober H-C. Clinical Improvement and Cost-effectiveness of CT-guided	Comparison of techniques.

Reference	Reason for Exclusion
Radiofrequency Sacroplasty (RFS) and Cement Sacroplasty (CSP) - a Prospective Randomised Comparison of Methods. Z Orthop Unfall 2019;157:524-33.	

*This SR of sacroplasty was excluded at full-text due to lack of RCT data. However, it does appear to include 2 non-randomized comparative cohort studies that may meet inclusion criteria for effectiveness

APPENDIX E. NEW FDA APPROVED DEVICES

The FDA results below are based on a limited search of the PMA and 510(k) databases using the following terms: spinal cement, augmentation cement, vertebroplasty, kyphoplasty, sacroplasty

Appendix Table E1: Summary of newly approved FDA devices since the 2016 signal update

Procedure/Device	Brief description	FDA Approval (Date)	Source
TRACKER Kyphoplasty System	The TRACKER Kyphoplasty System comprises the TRACKER-X, P (GSK System) and the TRACKER-I (GCD System). The TRACKER-I System is sold only as a System. The individual System Accessories are not sold separately. The GSK System consists of the TRACKER-P balloon expander and the TRACKER-X balloon catheter. The TRACKER-I is a cement dispenser kit intended for percutaneous access to bone and delivery of bone cement.	510(k) (12/04/2019)	https://www.accessdata.fda.gov/cdrh_docs/pdf19/K192335.pdf
SpineKure Kypholplasty System	The SpineKure Kyphoplasty System is designed to reduce spinal compression fracture and restore sagittal alignment by creating a space in the vertebral body to facilitate the insertion of bone cement. The SpineKure Kyphoplasty System is comprised of a Balloon Catheter, Balloon Inflator and Cement Delivery System (Accessories kit).	510(k) (05/29/2018)	https://www.accessdata.fda.gov/cdrh_docs/pdf17/K172871.pdf
Modified Winch Kyphoplasty (15 And 20 Mm) 11 Gauge Balloon Catheters	The Modified Winch Kyphoplasty (15 and 20 mm) 11 Gauge Balloon Catheters are intended to be used for the reduction and fixation of fractures and/or creation of a void in cancellous bone in the spine. This includes use during	510(k) (08/23/2017)	https://www.accessdata.fda.gov/cdrh_docs/pdf17/K172214.pdf

Procedure/Device	Brief description	FDA Approval (Date)	Source
	percutaneous vertebral augmentation. This system is to be used with cleared spinal polymethylmethacrylate (PMMA) bone cements for use during percutaneous vertebral augmentation, such as kyphoplasty.		
DCM Kyphoplasty System	The DCMKyphoplasty System is designed to reduce compression fracture and create a void in cancellous bone in the spine. This includes use during percutaneous vertebral augmentation. The system is to be used with cleared spinal polymethylmethacrylate (PMMA) bone cements indicated for use during percutaneous vertebral augmentation, such as kyphoplasty.	510(k) (02/06/2017)	https://www.accessdata.fda.gov/cdrh_docs/pdf16/K162283.pdf
VertaPlex HV High Viscosity Radiopaque Bone Cement	VertaPlex® HV High Viscosity Radiopaque Bone Cement is indicated for the fixation of pathological fractures of the vertebral body using vertebroplasty or kyphoplasty. It is also indicated for the fixation of pathological fractures of the sacral vertebral body or ala using sacral vertebroplasty or sacroplasty. P	510(k) (03/31/2020)	https://www.accessdata.fda.gov/cdrh_docs/pdf19/K192818.pdf

Appendix Table E2: Summary of FDA approved devices included in the 2016 signal update

Procedure/Device	Brief description	FDA Approval (Date)	Source
KIVA for VCF (Benvenue Medical, Santa Clara, CA)	A small coil-like flexible implant placed in the vertebral body that restores vertebral height and allows the direction of bone cement into the space surrounding the implant	FDA 510(k) clearance (January 2014)	http://benvenuemedical.com/products/ http://benvenuemedical.com/press-release/kiva-vcf-treatment-system-receives-fda-clearance-vertebral-compression-fractures/
Radiofrequency-targeted vertebral augmentation (RFTVA) (DFINE StabiliT	Targeted delivery of radiofrequency-activated warm, highly viscous bone	510k approved (December 2009)	https://www.accessdata.fda.gov/cdrh_docs/pdf9/K090986.pdf

Procedure/Device	Brief description	FDA Approval (Date)	Source
San Jose, CA)	cement PMMA using an articulating osteotome		
High-Viscosity cement vertebroplasty (HVCV) Confidence Spinal Cement System (DePuy Spine Inc, Raynham, MA, USA)	Modification of vertebroplasty designed to decrease cement leakage	FDA 510(k) clearance (December 2011)	https://www.accessdata.fda.gov/cdrh_docs/pdf11/K112907.pdf
Shield Kyphoplasty SOTEIRA, INC. 5 Whitcomb Avenue Ayer, MA 01432	includes a unilateral, steerable cavity creator and a self-expanding stent-like implant designed to direct PMMA cement flow for optimal placement during vertebral augmentation.	FDA 510(k) clearance (December 2011)	http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K093477
Crosstrees PVA Pod System	Uses a soft woven fabric pod that allows the flow of bone cement to be controlled as it is injected into the vertebral body.	FDA 510(k) clearance (August 2013)	https://www.accessdata.fda.gov/cdrh_docs/pdf13/K130089.pdf http://xtreesmed.com/crosstrees-system-solution.php

APPENDIX F. AMSTAR AND RISK OF BIAS EVALUATIONS

Appendix Table F1: Risk of bias evaluation for studies not included in summarized SRs

Methodological Principle	Liu 2019a	Li 2017	Liu 2019b	Firanescu 2019
Study design				
Randomized controlled trial	■	■	■	■
Prospective cohort study				
Retrospective cohort study				
Case-control				
Case-series				
Random sequence generation†	Unclear	Unclear	Yes	Yes
Concealed allocation†	Unclear	Unclear	Unclear	Yes
Intention to treat†	Yes	Unclear	Yes	Yes
Independent or blind assessment	No	No	No	Yes
Complete follow-up of ≥80%	Unclear	Unclear	Unclear	Yes
<10% difference in follow-up between groups	Unclear	Unclear	Unclear	Yes
Controlling for possible confounding‡	No	No	Unclear	Yes
Risk of Bias	**High**	**High**	**High**	**Low**

*Unclear indicates that the study had insufficient detail to determine whether criteria were met
†Applies only to randomized controlled trials.
‡Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed.
Notes:

- Liu 2019a (N=116):
  - Randomization sequence, allocation assessment: not reported
  - No specific statement of blinding provided, does not appear to do so
  - ITT not stated, but it is clear that all patients were analyzed in their assigned treatment groups
  - Baseline comparability cannot be assessed due non-robust reporting of baseline data
  - Attrition not described
  - Time of measurements NR
  - Poorly reported overall
- Li 2017 (N=80)
  - Randomization sequence, allocation assessment: not reported
  - No specific statement of blinding provided, does not appear to do so
  - Allocation not described
  - Not comparable at baseline (>10% difference in sex, ASA grade), VAS, ODI comparable
  - Attrition not described
  - Poorly reported overall
- Liu 2019b
  - Randomization by numerical form (assumed this mean a random numbers list?)
  - Allocation not described
  - ITT not stated, but it is clear that all patients were analyzed in their assigned treatment groups
  - No specific statement of blinding provided, does not appear to do so
  - Attrition not described
  - Baseline comparability cannot be assessed due non-robust reporting of baseline data
- Firanescu
  - Randomization using computer randomization in a block size of sic, randomization ratio 1:1
  - Statement of concealment
  - Blinded assessment: Participants, internists, nurses, and outcome assessors were blinded, but it was not possible to mask the interventional and diagnostic radiologists. However, for our purposes, this is not a concern because we are not interested in radiographic outcomes.

Appendix Table F2. AMSTAR evaluation of Buchbinder 2018 systematic review

	Question	Yes	Partial Yes	No	Notes
1	Did the research questions and inclusion criteria for the review include the components of PICO?	X			
2	Did the report of the review contain an explicit statement that the review methods were established prior to conduct of the review and did the report justify any significant deviations from the protocol?	X			
3	Did the review authors explain their selection of the study designs for inclusion in the review?	X			
4	Did the review authors use a comprehensive literature search strategy?		X		Unclear if authors consulted context experts or if grey literature was searched.
5	Did the review authors perform study selection in duplicate?	X			
6	Did the review authors perform data extraction in duplicate?	X			
7	Did the review authors provide a list of excluded studies and justify the exclusions?	X			
8	Did the review authors describe the included studies in adequate detail?	X			
9	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	X			
10	Did the review authors report on the sources of funding for the studies included in the review?	X			
11	If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	X			
12	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?			X	Authors did not provide an overall ROB determination for each of the individual trials, nor did they discuss the results in the context of the risk of bias associated with each trial
13	Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?			X	Authors did not provide an overall ROB determination for each of the individual trials, nor did they discuss the results in the context of the risk of bias associated with each trial

	Question	Yes	Partial Yes	No	Notes
14	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	X			
15	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?			X	Authors discussed performing an assessment of publication, but ultimately do not report on it.
16	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	X			

Appendix Table F3. AMSTAR evaluation of Hinde 2020 systematic review

	Question	Yes	Partial Yes	No	Notes
1	Did the research questions and inclusion criteria for the review include the components of PICO?	X			
2	Did the report of the review contain an explicit statement that the review methods were established prior to conduct of the review and did the report justify any significant deviations from the protocol?			X	
3	Did the review authors explain their selection of the study designs for inclusion in the review?			X	
4	Did the review authors use a comprehensive literature search strategy?	X			
5	Did the review authors perform study selection in duplicate?			X	Authors do not provided information re duplicate review/abstraction.
6	Did the review authors perform data extraction in duplicate?			X	Authors do not provided information re duplicate review/abstraction.
7	Did the review authors provide a list of excluded studies and justify the exclusions?		X		Provided reasons for exclusion and number excluded, but no citations.
8	Did the review authors describe the included studies in adequate detail?		X		
9	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	X			

	Question	Yes	Partial Yes	No	Notes
10	Did the review authors report on the sources of funding for the studies included in the review?			X	
11	If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	X			
12	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?			X	
13	Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?			X	
14	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?		X		Authors discussed heterogeneity and performed sensitivity analysis but did not provide a robust discussion of this.
15	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	X			
16	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	X			

APPENDIX G. CITATIONS FOR STUDIES INCLUDED IN 2016 SIGNAL UPDATE

1. Vertebral Augmentation Involving Vertebroplasty or Kyphoplasty for Cancer-Related Vertebral Compression Fractures: A Systematic Review. Ont Health Technol Assess Ser 2016;16:1-202.
2. Berenson J, Pflugmacher R, Jarzem P, et al. Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial. Lancet Oncol 2011;12:225-35.
3. Buchbinder R, Golmohammadi K, Johnston RV, et al. Percutaneous vertebroplasty for osteoporotic vertebral compression fracture. Cochrane Database Syst Rev 2015;4:CD006349.
4. Clark W, Bird P, Gonski P, et al. Safety and efficacy of vertebroplasty for acute painful osteoporotic fractures (VAPOUR): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet 2016;388:1408-16.
5. Fritzell P, Ohlin A, Borgstrom F. Cost-effectiveness of balloon kyphoplasty versus standard medical treatment in patients with osteoporotic vertebral compression fracture: a Swedish multicenter randomized controlled trial with 2-year follow-up. Spine (Phila Pa 1976) 2011;36:2243-51.
6. Li L, Ren J, Liu J, et al. Results of Vertebral Augmentation Treatment for Patients of Painful Osteoporotic Vertebral Compression Fractures: A Meta-Analysis of Eight Randomized Controlled Trials. PLoS One 2015;10:e0138126.
7. Stevenson M, Gomersall T, Lloyd Jones M, et al. Percutaneous vertebroplasty and percutaneous balloon kyphoplasty for the treatment of osteoporotic vertebral fractures: a systematic review and cost-effectiveness analysis. Health Technol Assess 2014;18:1-290.
8. Yang EZ, Xu JG, Huang GZ, et al. Percutaneous Vertebroplasty Versus Conservative Treatment in Aged Patients with Acute Osteoporotic Vertebral Compression Fractures: A Prospective Randomized Controlled Clinical Study. Spine (Phila Pa 1976) 2016;41:653-60.