Washington State Health Care Authority

WASHINGTON STATE HEALTH CARE AUTHORITY

Health Technology Assessment Program

Peer Review and Public Comments and Responses

Vertebroplasty, Kyphoplasty and Sacroplasty

Date: November 4, 2010

Health Technology Assessment

Vertebroplasty, kyphoplasty, and sacroplasty

Peer Review and Public Comments and Responses

November 4, 2010

Note: Spectrum is an independent vendor contracted to produce evidence assessment reports for WA HTA program. For transparency, all comments received during the comments process are included. However, comments related to program decisions, process, or other matters not pertaining to the report are acknowledged through inclusion, but are not within the scope of response for report accuracy and completeness.

Spectrum Research response to peer review comments

Michael J. Lee, M.D., Assistant Professor, Department of Orthopedics and Sports Medicine, University of Washington

Comment 1 response (p. 32): Added additional statement that fractures are multi-factorial in origin and occur in the absence of cement augmentation.

Comment 2 response (p. 33): Added additional statement that surgical failures are of concern in patients with low bone mineral density.

Jeffrey G. Jarvik, M.D., MPH, Professor, Department of Radiology, University of Washington

Comment 1 response (p. 28): Deleted statements about kyphoplasty requiring general anesthesia and overnight hospital stay.

Comment 2 response (p. 30): ADR has been corrected to ACR.

Comment 3 response (p. 20): This error in numbering of the key questions has been corrected.

Comment 4 response: Co-interventions include ancillary treatments such as physical therapy and pain medications. Because such treatments can influence pain and functional outcomes, they should be comparable in both arms of the trial. In order to meet the criterion for equivalent co-interventions, the published paper should state that supplementary treatment is applied equally to treatment and control groups. In the Kallmes paper, no description of how co-interventions (including pain mediation) were applied was included. The Buchbinder paper stated that treatment decisions were made at the discretion of the treating physician, which implies that co-interventions were not standardized.

Comment 5 response (p. 50): In the INVEST trial, local anesthetic was used in both treatment and control groups, and was therefore a constant. In the Australian trial, local anesthetic injection was not used (see next response).

Comment 6 response (p. 56): As stated by Buchbinder and Kallmes in a published comment:

> The assertion that in both trials vertebroplasty was not compared with a true placebo or sham procedure is not correct. As is clearly described in our published protocol and results papers, a dry needle was inserted in the Australian trial; no anesthetic was injected into the facet joint

or periosteum. (pp. 242-243 in Buchbinder, R, Kallmes, DF (2010). *Vertebroplasty: when randomized placebo-controlled trial results clash with common belief.* Spine J. 10(3): 241-3.)

Comment 7 response (p. 77): See responses to comments 5 & 6.

Comment 8 response (p. 79): Revised the text to remove the reference to decreased opiate use in all groups.

Comment 9 response (p. 113): We noted in the report that there were no statistically significant group differences in either pain or functional outcomes in these two RCTs, and that there was a trend toward greater achievement of a clinically important reduction in pain in the vertebroplasty group. We have added a short discussion of potential unblinding in the Kallmes study and its potential effect on perceived pain.

Comment 10 response (p. 121): As there are significant differences in study design between the sham controlled trials (Kallmes, Buchbinder) and trials comparing vertebroplasty to conservative treatment (Klazen, Rousing, Voormolen), it was not appropriate to consider them together. Separate statements for the sham controlled studies and the studies comparing vertebroplasty with conservative care have been added. The overall strength of evidence for both categories of study is low.

Brian M. Drew, M.D., Assistant Clinical Professor, Department of Surgery, McMaster University, Medical Director, Hamilton General Hospitals Spine Unit

Comment 1 response (pp. 26-29): We have discussed issues regarding complications associated with non-surgical management in the section entitled Alternative Treatments.

Comment 2 response (p. 28): See response to Jarvik comment #1.

Comment 3 response (p. 29): We revised this section to state that the only significant difference in the two procedures is the additional equipment and operative time.

Comment 5 response (pp. 32-33): We have attempted to address some of the issues about timing of surgery in the discussion of Key Question 3 (differential efficacy) in the discussion of acute vs. chronic fractures.

Comment 6 response (p. 56):

- Sham surgery: see response to Jarvik comment #5 & 6.
- Proportion of eligible patients enrolled: according to the enrollment numbers given in the published papers describing these RCTs, 35.4% of eligible patients were enrolled in the Buchbinder study, and 30.4% of eligible patients were enrolled in the Kallmes study.

Spectrum Research response to public comments

Clinician/professional organizations

Society of Interventional Radiology (SIR)

Comments are attached in the Appendix. No apparent issues were raised that are specific to the content of this HTA.

North American Spine Society (NASS)

Comments are attached in the Appendix. No apparent issues were raised that are specific to the content of this HTA.

Industry

Stryker Instruments

Comment regarding recruitment biases for sham-controlled randomized controlled trials: The potential for recruitment bias is not limited to sham-controlled RCTs. We noted in the report that from 30-35% of eligible patients were enrolled in the sham-controlled RCTs. These proportions were similar in unblinded RCTs: the FREE and VERTOS 2 studies reported enrollment of 32% and 33% of eligible patients, respectively.

Comment regarding need for confirmatory studies in addition to the FREE study: The determination of strength of evidence used in the technology assessment is based on several criteria: quantity and quality of studies, and consistency of findings (see Appendix D). Using this framework, more than one confirming study is needed to meet the quantity criterion.

Comment regarding restriction to comparative studies: The scope of the report was largely focused on comparative studies, since issues of efficacy and effectiveness can only be addressed with studies that compare an intervention to an alternative treatment. Non-comparative studies were only considered for descriptions of safety outcomes (since comparative studies may not capture these) or for procedures for which no comparative studies were found (sacroplasty).

Medtronic, Inc.

Comment 3: Our report covers information about effectiveness and safety extensively. The AAOS document was not available in time for inclusion into the HTA. It is noted that while kyphoplasty is recommended as an option in this document, the strength of recommendation is rated as “weak.”

Comment 4: See response to Jarvik comment #1.

Comment 5: Findings from the CAFE trial do not meet our inclusion criteria (full-length studies published in peer-reviewed journals).

Comment 6:

- The Kumar study was not yet published at the time of our literature search.
- The Komp study does not meet our inclusion criteria, as it is not published in English.
- The Dong study was missed by our literature search. After reviewing the study, we concluded that we would have excluded it from our report because it includes no comparisons of vertebroplasty to kyphoplasty with respect to reported pain. In our report, we focused on summarizing commonly-studied outcomes across studies, and this study did not include analyses of our primary outcomes of interest (pain and physical functioning); its primary purpose was to examine lung function. Addition of this small, low-quality, nonrandomized study would not change our conclusions or strength of evidence.

Comment 8: As described in the report, we did not include studies that used administrative databases. The reasoning for exclusion of such studies is outlined on page 56 of the report.

Comment 9: The Edidin study did not meet our inclusion criteria (full-length studies published in peer-reviewed journals).

Comment 10: The Hulme review was not included because additional, higher quality comparative studies than those that were included in that report were available. As stated in the methods section, "Reports that were published between 2007 and 2010 and whose search ending dates were 2006 or later were considered for inclusion, given that additional comparative studies have been published since 2007."

Comment 13:

- Additional HTAs not included:
    - The CTAF HTAs are summarized in section 1.4 of the report.
    - The Ontario evidence update (October 2010) was not available at the time of our search.
    - The reports by Hayes and ECRI are not publicly available.
- Medicare coverage: Reporting of the National Coverage Determination (NCD) is required for Washington State HTAs, and local coverage determinations (LCD) are not. The LCD for the region which includes Washington State is logically the most relevant to the Washington State HTA process.
- Inclusion of policies of additional payers: Reporting on policies of two bellwether payers is required by the Washington State HTAP. Policies for Cigna and Aetna were included in the report.

- Errors in description of Regence policy: The description of the Regence policy for coverage of vertebroplasty and kyphoplasty has been corrected.

Peer review comments

Michael J. Lee, M.D., Assistant Professor, Department of Orthopedics and Sports Medicine, University of Washington

INTRODUCTION Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Overview of topic is adequate?
- Topic of assessment is important to address?
- Public policy and clinical relevance are well defined?

The overview of this topic is adequate. The topic of assessment, particularly in light of recent literature is very important to address. Public policy and clinical relevance are well defined.

BACKGROUND Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Content of literature review/background is sufficient?
-

The content of this literature review is sufficient.

Content of literature

Page 32	Line

Regarding statements of new fracture after percutaneous cement augmentation, it should be emphasized that new fragility fractures of the spine occur after conservative treatment of fracture. The etiology of new osteoporotic compression fracture after initial fracture is multi-factorial whether or not the fracture has been treated with cement augmentation. The rates of new fracture after percutaneous cement augmentation need to be compared to the rates of new fracture after conservative treatment in a controlled fashion to determine if there is an associative relationship.

Page 33	Line

Regarding the risks of lumbar fusion for the treatment of osteoporotic compression fractures: In addition the inherent risks and costs of invasive surgery, it should be noted that these risks are particularly elevated in this patient population. From a technical perspective, it is challenging to

obtain surgical fixation in the osteoporotic spine. It has been shown in a multitude of studies that pedicle screw fixation is much less rigid in specimens with lower bone mineral density. Thus, there is a substantial concern for possible screw pullout, other failures of fixation, or junctional failure. Any of these complications can lead to additional surgery. The invasiveness of these surgeries and the elevated medical and surgical risks inherent to this patient population have led clinicians to seek out less invasive approaches to treating these fractures.

REPORT OBJECTIVES & KEY QUESTIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Aims/objectives clearly address relevant policy and clinical issue?
- Key questions clearly defined and adequate for achieving aims?

Aims clearly address relevant policy and clinical issues. Key questions are clearly defined.

METHODS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Method for identifying relevant studies is adequate?
- Criteria for the inclusion and exclusion of studies is appropriate?
- Method for Level of Evidence (LoE) rating is appropriate and clearly explained?
- Data abstraction and analysis/review are adequate?

Methods are adequate, and description of all studies described is detailed and exhaustive. Level Of Evidence is clearly explained. Analysis and review are adequate.

RESULTS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Amount of detail presented in the results section appropriate?
- Key questions are answered?
- Figures, tables and appendices clear and easy to read?
- Implications of the major findings clearly stated?
- Have gaps in the literature been dealt with adequately?
- Recommendations address limitations of literature?

The detail presented is thorough and exhaustive. Key questions are answered and figures, tables and appendices are easy to read, though they are many in number. Gaps in the literature have been appropriately addressed, and recommendations do address the limitations of the literature.

CONCLUSIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Are the conclusions reached valid?

The conclusions reached are valid. They well represent the current literature

OVERALL PRESENTATION and RELEVANCY Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Is the review well structured and organized?
- Are the main points clearly presented?
- Is it relevant to clinical medicine?
- Is it important for public policy or public health?

This is an exhaustive detailed report which dissects the literature in this topic. The main points are clearly presented. In light of recent literature, it is of clear relevance to clinical medicine and for public policy and public health.

While the literature at this time is insufficient to conclude unequivocally on the clinical effectiveness, clinical efficacy or cost effectiveness of percutaneous cement augmentation, it is important to note that failure of proof is not synonymous to proof of failure.

Further research is needed to better define the roles these procedures may play in clinical medicine.

QUALITY OF REPORT

Quality Of the Report (Click in the gray box to make your selection)
Superior x
Good ☐
Fair ☐
Poor ☐

Jeffrey G. Jarvik, M.D., MPH, Professor, Department of Radiology, University of Washington

INTRODUCTION Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Overview of topic is adequate?
- Topic of assessment is important to address?
- Public policy and clinical relevance are well defined?

The overview is very good. The authors describe the 3 augmentation procedures being considered. The key questions follow and in the next section, the methods for evaluating comparative effectiveness are concisely described.

BACKGROUND Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Content of literature review/background is sufficient?
-

The authors review the rapid rise in both the number of vertebral augmentation procedures as well as the cost of those procedures to Washington State. The authors make a clear case as to why this is an important topic.

It identifies all of the major scientific studies investigating vertebral augmentation, highlighting the two recent pivotal studies that demonstrated no benefit of vertebroplasty when compared with local anesthetic injection.

Page 28 Line 12

Kyphoplasty is now being performed as an outpatient procedure without general anesthesia.

Page 30 Line 18

Under “Contraindications for vertebroplasty, kyphoplasty and sacroplasty”, the “ADR”is listed multiple times, but this should probably be the “ACR.”

REPORT OBJECTIVES & KEY QUESTIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Aims/objectives clearly address relevant policy and clinical issue?
- Key questions clearly defined and adequate for achieving aims?

Page 19 Line bottom

The report's objectives/aims are clearly stated on p. 19. The key questions are well defined and appropriate for achieving the aims.

Page 20 Line

It's not clear why the key questions, when they are repeated here, have different numbers than when they are listed in the table from p14-18, or when listed in the text from p. 9-13.

METHODS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Method for identifying relevant studies is adequate?
- Criteria for the inclusion and exclusion of studies is appropriate?
- Method for Level of Evidence (LoE) rating is appropriate and clearly explained?
- Data abstraction and analysis/review are adequate?

Overall, the methods for identifying studies was appropriate and adequate. As far as I could tell, no important studies were left out of the review. The inclusion and exclusion criteria were appropriate. The methods for LoE rating were fairly clearly explained in Appendices D and E. However, the authors could better clarify what is meant by "co-interventions applied equally" as is listed in Appendix D, p. 8. This is important because it is the only criterion that the RCTs of Buchbinder and Kallmes fail to meet. The description of the data abstraction and analysis/review are adequate, except as noted below.

Page 50 Line

2.1.1 Comparator: The authors mention that sham treatment was a comparator, but do not describe other injection treatments, which was the comparator in the two NEJM RCTs. While the Australian RCT describes this comparator as a "sham", the INVEST trial does not, and in fact, local anesthetic injection may be regarded as a viable alternative treatment, not a sham, and worthy of consideration for comparative effectiveness evaluations.

Page 56 Line

Section 2.2.2 Critical appraisal: I believe that the authors are incorrect in describing the Buchbinder trial as not having used local anesthetic. It clearly states in their methods paper (BMC Musculoskeletal Disorders 9; 156, 2008) that the sham procedure was identical to the actual vertebroplasty up to the placement of the trocar against the lamina. Thus, lidocaine was infiltrated subcutaneously and probably deeper, including the laminar periosteum. The authors of

the review could clarify this point with Dr. Buchbinder. In addition to p. 56, the section "Buchbinder 2009" on p. 57 also needs to be amended to reflect this correction.

RESULTS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Amount of detail presented in the results section appropriate?
- Key questions are answered?
- Figures, tables and appendices clear and easy to read?
- Implications of the major findings clearly stated?
- Have gaps in the literature been dealt with adequately?
- Recommendations address limitations of literature?

The amount of detail presented is appropriate and all the key questions are addressed. The figures/tables and appendices are clear, easy to read and helpful. Gaps in the literature were clearly acknowledged.

Page 77 Line

The authors of the report repeatedly use the term "sham" to describe the comparator in both the Buchbinder and Kallmes trials, yet, as described above, the comparator in both trials consisted of a local anesthetic injection that should be considered a viable clinical alternative and not a sham. Their report should be amended to reflect this.

Page 79 Line

The authors describe a similar decrease in opiate use in both the vertebroplasty and control groups for the Kallmes study, but this was not the case. As can be seen from their figure on p.79, opiate use in the vertebroplasty group remained essentially unchanged at 1 month (56% vs. 54%) while it decreased in the control group (63% to 43%). This is important, because higher opiate use could influence pain perception.

CONCLUSIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Are the conclusions reached valid?
- In general, the conclusions are valid. See below for some specific comments

Page 113 Line

Key question 1: Vertebroplasty efficacy

The authors do not mention that the RCTs by Kallmes and Buchbinder were much less ambiguous regarding the lack of functional improvement as compared with pain. Their

conclusion should reflect this difference between pain and functional outcomes. This is potentially important since pain may be much more influenced by unblinding, which could have accounted for at least a portion of the greater improvement in pain in the Kallmes study,

Page 121 Line

It's not clear why the evidence for vertebroplasty is rated as low and not moderate. The criteria for evidence quality, as described in Appendix D, p.9, indicates that both the quality and quantity criteria were met. However, the summary of evidence table on p.121 indicates that the quantity criteria were not met. The quantity criterion is that there be at least 3 adequately powered studies. The RCTs by Kallmes, Buchbinder and Klazen were all adequately powered, although not consistent in their conclusions (understandably because of differences in study design). Nonetheless, they should have satisfied the quantity criterion and thus, with 2 of 3 criteria satisfied, merited a moderate SoE.

OVERALL PRESENTATION and RELEVANCY Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Is the review well structured and organized?
- Are the main points clearly presented?
- Is it relevant to clinical medicine?
- Is it important for public policy or public health?
-

The review is quite well structured and the main points are clearly presented. The review is extremely relevant to clinical medicine and highly important for public policy.

QUALITY OF REPORT

Quality Of the Report
(Click in the gray box to make your selection)

Superior ☐

Good ☒

Fair ☐

Poor ☐

Brian M. Drew, M.D., Assistant Clinical Professor, Department of Surgery, McMaster University, Medical Director, Hamilton General Hospitals Spine Unit

INTRODUCTION Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Overview of topic is adequate?
- Topic of assessment is important to address?
- Public policy and clinical relevance are well defined?

Page 6-10 Line

The review of compression fractures and osteoporosis was accurate. The summary of the various cementoplasty techniques and procedures was also accurate and well done.

The efficacy and effectiveness issues are essential for clinicians to understand. Clinicians can then understand what the potential benefits will be for their patients. These issues were introduced concisely and accurately.

The introduction to the issues regarding safety was well done. It was comprehensive. Accurate and objective knowledge of the safety of the 3 procedures will assist clinicians in helping patients make informed decisions when deciding whether to proceed with a procedure or when consenting for a procedure.

Page 19 Line

It was important to highlight that the patient population has specific health issues and morbidities that pre-date the fracture or occur as a result of the fracture. It was equally important to comment of the potential consequences of leaving a fracture untreated. It was also mentioned that the cementoplasty techniques are not indicated for osteoporosis alone but also for certain tumor-related fractures.

Page Line

Overall, the clinical relevance of the various cementoplasty procedures were designed to address was outlined well and accurately represented.

BACKGROUND Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Content of literature review/background is sufficient?

Page 26-29 Line

The review of osteoporotic and malignant fractures was reviewed well.

I think the issues concerning conventional treatment need to be highlighted or emphasized to a greater degree. Particularly the complications and morbidity associated with the various form of non-surgical management.

Page 28 Line

The technology paragraph states that kyphoplasty almost always requires general anaesthesia and at least one overnight stay. Consideration should be given to the fact that 1 and sometimes 2 level disease can be accomplished under local anaesthesia and conscious sedation. Lumbar and lower thoracic spine fractures can be treated under spinal anaesthesia. At my institution it is very rare that a patient stays overnight, most go home the same day. This occurs with most single level fractures and often with 2 or 3 level fractures. The patient's co-morbidities may dictate admission for an overnight stay but this is the exception and not the rule for most of the kyphoplasties that are done at my institution.

Page 29 Line 2nd paragraph

See above comments regarding the need for general anaesthesia and an overnight stay. Also while I agree that the kyphoplasty procedure requires the inflatable bone tamp, the other steps in the procedure are essentially similar to vertebroplasty. The placement of the osseous introducers or cannulae are very similar as is the cement injection steps. The addition of the bone tamp is really the only significant difference. So the ease vertebroplasty over kyphoplasty is relatively small.

REPORT OBJECTIVES & KEY QUESTIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Aims/objectives clearly address relevant policy and clinical issue?
- Key questions clearly defined and adequate for achieving aims?

Page 31-32 Line

The issues with regard to cement leakage were reviewed well.

Page 32-33 Line

The topic of conservative treatment was highlighted fairly well for fractures that do not heal. This could be expanded on more as this is for the most part the indication for the cementoplasty techniques and ill defined in the literature as to the timing of surgery.

Page 47-51 Line

This section reviews the various studies that are currently underway. This adds to the health technology assessments comprehensiveness and will hopefully assist in the future with helping to answer some of the key questions.

METHODS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Method for identifying relevant studies is adequate?
- Criteria for the inclusion and exclusion of studies is appropriate?
- Method for Level of Evidence (LoE) rating is appropriate and clearly explained?
- Data abstraction and analysis/review are adequate?

The method in which the systematic literature review was done was quite comprehensive. The tables and flow charts assisted as a good summary tool.

The LoE was excellent and the summary in Appendix D was helpful.

2.2.1 demonstrated the relationship of the LoE to the key questions nicely.

2.2.2 and 2.3.1 This was the section discussing vertebroplasty compared to sham surgery. It was important to raise the issue of whether the local anaesthesia was truly a sham. Also the assessment quoted that 30-36% of eligible patients were enrolled. I have heard that this was as low as 20%. The authors that quoted this number may have been wrong as I am not sure of their source.

Page 57-62 Line

The review of the RCT's was comprehensive and accurate.

Page 62-64 Line

The more brief review of the cohort studies was appropriate in length and depth.

RESULTS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Amount of detail presented in the results section appropriate?
- Key questions are answered?
- Figures, tables and appendices clear and easy to read?
- Implications of the major findings clearly stated?
- Have gaps in the literature been dealt with adequately?
- Recommendations address limitations of literature?

The amount of detail presented was comprehensive, summarizing a large body of literature but in a succinct manner. The various figures, tables and appendices summarized the topics well and were easy and clear to read.

The strengths and limitations in the literature were clearly identified. The major points and the conclusions of the higher quality studies were repetitively commented on. This added to the clarity of the assessment. All gaps in the literature were identified. The section on studies that are currently underway addresses some of the gaps in the literature.

CONCLUSIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Are the conclusions reached valid?

Based on the available evidence reviewed, the conclusions that were presented are fair and valid. They accurately reflect the current literature. The review was objective and systematic in its analysis. The more significant clinical conclusions regarding efficacy, effectiveness and safety of the three procedures were reviewed in more depth which appropriately reflects their importance.

OVERALL PRESENTATION and RELEVANCY Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Is the review well structured and organized?
- Are the main points clearly presented?
- Is it relevant to clinical medicine?
- Is it important for public policy or public health?

The review was well structured and organized. The table of contents and list of figures and tables made it easy to locate content. The subheadings also assisted in locating content and read.

I had some difficulty with the sections listed for the reviewers to evaluate. There was a background, results and methods (under evidence) section that were clearly titled. The form or guide with the questions listed to keep in mind also seemed to indicate that would be a conclusion section which I realized did not exist as I finished reading the report. The reviewers guide stated "while reviewing this section". This was only slightly and temporarily confusing and overall did not take away from the organization of the document as a whole.

The main points were presented in a clear fashion. They were repeated several times in various sections which added strength to it.

I believe this topic is extremely relevant. Vertebral compression fractures are a public health issue which is large now and will increase and the population ages. Current medical or non-surgical treatments are failing to prevent or significantly reverse osteoporosis. The morbidity of untreated fractures should not be overlooked. The dangers of prolonged bed rest or immobility, spinal deformity, pain, psychological impacts like patient depression and caregiver stress can not be overlooked. I think this issue could be emphasized to a greater degree in the assessment.

Despite the lack of strong trials, physicians tend to believe in the effectiveness and safety of these procedures. More patients and their families are beginning to advocate for their own care. The issues such as pain, stress, and depression tend to push patients and their families to request physicians to perform these procedures. Upcoming trials will help answer some of the question regarding effectiveness and safety etc. but until then physicians are left with the art of treating these patients so the review of this topic is timely and of great importance.

QUALITY OF REPORT

I could not click in the gray box above but rated the report as superior.

Public comments

Clinician/professional organizations

Society of Interventional Radiology (SIR): See Appendix pages 1-29

North American Spine Society (NASS): See Appendix pages 30-35

Industry

Stryker Instruments: See Appendix pages 36-41

Medtronic, Inc.: See Appendix pages 42-267

October 22, 2010

Health Technology Assessment Program
Washington State Health Care Authority
P.O. Box 42712
Olympia, WA 98504-2712

Submitted electronically at: shtap@hca.wa.gov

RE: Draft Assessment- Vertebroplasty, Kyphoplasty, Sacroplasty

Dear Colleague,

The Society of Interventional Radiology (SIR) appreciates the opportunity to express our views in regard to the referenced draft technology assessment. At least one of our members will be present at the December 10th public meeting on this assessment.

The American College of Radiology (ACR) endorses the opinions expressed in this letter.

The Washington State Radiology Society (WSRS) has also reviewed this letter. Acting President Justin P. Smith, MD, has communicated to SIR that the WSRS endorses the views expressed herein.

The SIR is a professional association that represents 4,700 members who are practicing in the specialty of vascular and interventional radiology. The Society is dedicated to improving public health through pioneering advances in minimally-invasive, image-guided therapy. Our members are at the forefront of new and minimally invasive therapies to treat an array of diseases and conditions without surgery. Interventional radiology treatments have become first-line care for a wide variety of conditions and patients, including osteoporosis patients with spinal fractures, peripheral arterial disease, deep vein thrombosis, uterine fibroids, and stroke patients.

The 34,000 members of the ACR include radiologists, radiation oncologists, medical physicists, interventional radiologists and nuclear medicine physicians. For over three quarters of a century, the ACR has devoted its resources to making imaging safe, effective and accessible to those who need it. The mission of the ACR is to serve patients and society by maximizing the value of radiology, radiation oncology, interventional radiology, nuclear medicine and medical physics by advancing the science of radiology, improving the quality of patient care, positively influencing the socio-economics of the practice of radiology, providing continuing education for radiology and allied health professions and conducting research for the future of radiology.

This comment letter is organized into four sections:

- Past Research
- 2009 clinical trials published in the *New England Journal of Medicine*
- New and Ongoing Research
- Summary and our clinical suggestions

We are also attaching to this letter several documents that are materially relevant to our position, and might add to your review.

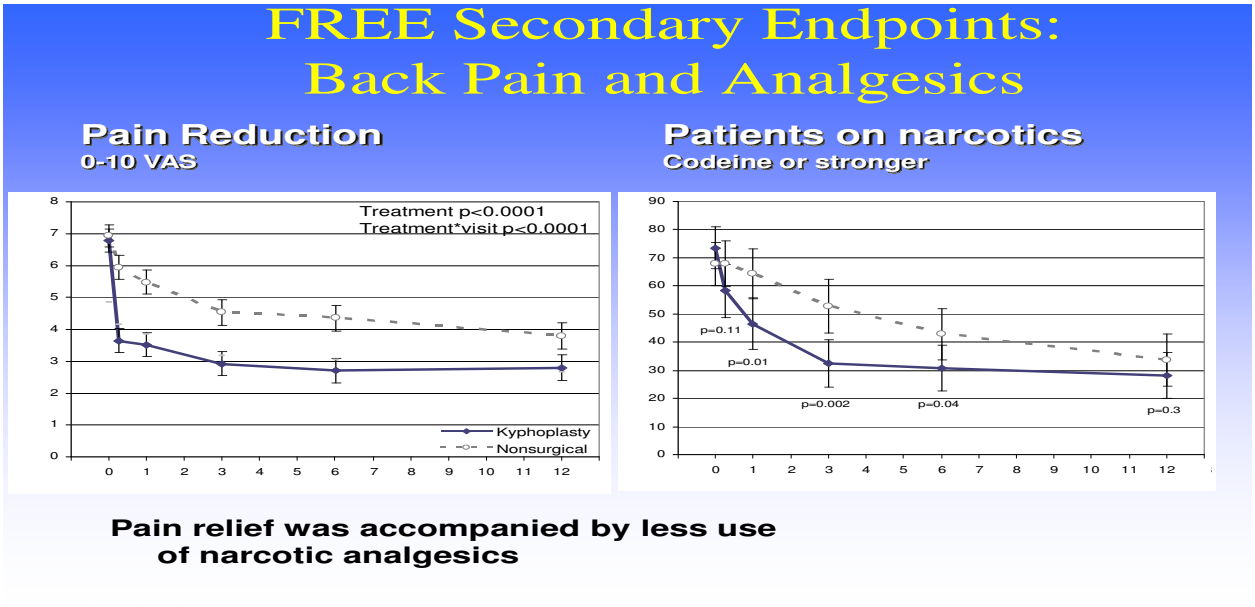
Past Research

Vertebral Compression Fractures (VCF) are a significant health burden on the Medicare population. Estimates are that over 700,000 VCFs occur annually in the United States as a result of osteoporotic disease (Melton, et al, 1989). The devices/cement used in vertebroplasty and kyphoplasty are FDA- approved, and the procedures have gained wide acceptance in the treatment of patients with painful VCFs caused by osteoporosis, multiple myeloma, vertebral hemangiomas, or metastases. Beyond pain and immobility, other clinical consequences of VCFs include pulmonary dysfunction, chronic spinal deformity, chronic pain, and depression. (Silverman, 1992). Past analysis has shown that mortality risk increases by 23% following the onset of a VCF(s) (Kado, et al 1999).

To date, several key studies have shown that vertebral augmentation procedures result in greater pain relief than conservative medical management. Typical of these studies, Diamond, et al (2006) concluded that "the analgesic benefit of percutaneous vertebroplasty and the low complication rates suggest that it is a useful therapy for acute painful osteoporotic vertebral fractures."

McGraw, et al (2002), followed 100 patients who underwent vertebroplasty over a 35-month period. Ninety-seven patients (97%) reported significant pain relief 24 hours after treatment. Mean follow-up duration was 21.5 months (6-44 mo) in 99 patients. Ninety-two patients (93%) reported significant improvement in back pain previously associated with their compression fractures as well as improved ambulatory ability. Before vertebroplasty, the VAS score for the 99 patients was 8.91 +/- 1.12 compared to a score of 2.02 +/- 1.95 at follow-up. The mean difference in VAS scores was significant (P <.0001).

In the FREE Trial, Wardlaw and colleagues prospectively randomized 300 patients into two groups: kyphoplasty treatment and conservative care. Patients in the kyphoplasty group showed an average VAS improvement of 5.2 points at 1-month vs the conservative care group.
They also show sustained improvements at 3 months, 6 months and 12 months. The kyphoplasty group also required less narcotic use to control their pain than the conservative care group. According to lead researchers Wardlaw and Van Meirheeghe, the two year results of FREE will soon be available and will include information on restoration of height by kyphoplasty.



Ashraf, Unpublished Presentation, 2010

The available scientific literature demonstrates that in appropriate patients, vertebroplasty and kyphoplasty are effective treatments for osteoporotic vertebral fractures. However, we acknowledge that performing a randomized control trial is difficult with this procedure, and with this patient population. Accordingly, we believe it is incumbent to look closely at the 2009 studies of Dr. Kallmes and Dr. Buchbinder cited in your review.

2009 New England Journal of Medicine Studies

In the draft assessment, the HTA notes the two studies by researchers David F. Kallmes, MD and Rachelle Buchbinder, PhD that were published in the August 6, 2009, edition of the *New England Journal of Medicine*. The Society endorses the value of evidence-based medicine and randomized control trials, but we also are of the opinion that weakness in the design of these two NEJM studies, past studies indicating that vertebroplasty is effective, new research, and clinical experience need to be considered also. In sum, our position is that it is very premature- and possibly incorrect- to conclude that vertebroplasty is no better than a control sham procedure (trigger point, facet injection) in treating patients.

We respectfully urge the HTA to review these studies in the context of a much greater body of evidence that supports the efficacy and safety of vertebral augmentation.

In 2007, the *Society's Journal of Vascular Interventional Radiology* originally published the "Position Statement on Percutaneous Vertebral Augmentation: A Consensus Statement Developed by the 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" on the safety and efficacy of

spine augmentation, and specifically vertebroplasty and kyphoplasty provided to appropriate patients when performed according to published standards (2007; 18:325-330). SIR is also currently working with other societies to update this 2007 Consensus Position Statement, and a revised Position Statement is expected to be public in early 2011, possibly by the end of this year.

With respect to the two recent studies questioning vertebroplasty, in a November 24, 2009, SIR Commentary on Vertebroplasty and the August Studies in the *New England Journal of Medicine*, SIR states "that several important factors need to be considered prior to accepting these two studies as fact negative (that vertebroplasty is no better than a sham control in relieving pain in patients with symptomatic compression fractures)." Criticisms of both studies include the small numbers of patients treated; the small percentage of eligible patients who were actually enrolled in the trial; inclusion of patients with milder degrees of pain and disability than are usually treated in a typical practice; the small amount of cement injected; treatment of patients with chronic compression fractures; the incomplete use of MRI or CT to confirm that the fracture was the likely source of pain; and the high rate of crossover from placebo to vertebroplasty in one of the studies.

Criticism has also come from one of the studies' investigators. William Clark, MD, St. George Private Hospital, Sydney, Australia, and an investigator with the Kallmes study, said he regarded that study as "meaningless." In addition, he called the Buchbinder study "a rush to judgment on 'science-based medicine' without applying scientific technique in appraising the studies" in comments posted to the Arthritis Today Web site. Clark noted numerous flaws in the studies, indicating they had "inappropriate patient selection, terrible recruitment and selection bias with the majority not followed."

SIR believes that the results of these trials are discordant with the more than 15 years of accumulated medical literature clinically confirming the benefits of spine augmentation, specifically vertebroplasty; many of which were large prospective trials. Hundreds of thousands of patients have greatly benefited from vertebroplasty with almost complete resolution of their pain. Tens of thousands of patients on intravenous narcotics have been promptly discharged from the hospital virtually pain free following their treatment. Because the Kallmes and Buchbinder studies are so discordant with the body of literature and personal experience of most physicians who treat patients with painful compression fractures, closer scrutiny of the two studies is warranted.

New and Ongoing Research

On August 10, 2010, the results of the VERTOS II open-label randomized control trial were published online in *The Lancet.* VERTOS II provides markedly different results from Kallmes and Buchbinder.

In their findings, the VERTOS II authors note that vertebroplasty resulted in better pain relief after one, three, and six months and one year ($P<0.001$, $P<0.001$, $P=0.025$, and $P=0.014$,

respectively) over conservative treatment. No serious complications or adverse events were reported. The incidence of new compression fractures was lower in the vertebroplasty group, although not significantly different from the conservative care (control) group.

The VERTOS II study additionally notes that vertebroplasty appears to be a cost effective treatment. The "adjusted trial-based incremental cost-effectiveness ratio for vertebroplasty, as compared to conservative treatment, was €22,685 per QALY gained." While we concur that many VCFs heal on their own through conservative treatment, the long term costs of conservative care, pain narcotics, extended hospitalizations, risks of deep vein thrombosis, pressure sores, and often the need for skilled nursing (or extensive family care) must be acknowledged as costs of conservative care. As one of our Washington state member physicians communicated to SIR, "the typical patient is discharged from the hospital the next day after vertebroplasty. At our hospital, the hospitalists rely on this procedure to get their patients out of bed and discharged." This is a major cost benefit compared to conservative care.

The principle limitation of the VERTOS II study is the lack of a sham control. However, this limitation deserves closer analysis. In fact, Dr. Kallmes has recently stopped using the term sham for patients that receive medial branch block and has changed it to "control intervention." However, we in the medical provider community would comment that it is extremely difficult to recruit patients to a sham controlled trial, and it may not be feasible to conduct a study of this type. Of note, in the Kallmes study, many US institutions would not endorse sham trials and many investigators remain wary of sham trials.

Therefore, the VERTOS II study represents the highest quality of data regarding percutaneous vertebroplasty for symptomatic vertebral compression fractures. The strength of this study is the on-going positive benefit at the one year follow up period. In addition to long term pain relief, this study demonstrated a very rapid pain relief. Short term pain outcome is vitally important in and of itself as patients with disabling acute pain are at significant risk of further complications and are not candidates for long term conservative therapy.

Ongoing analysis of Medicare claims data also indicates that patients who do not receive surgical care appear to have an increased risk of death in the period after a VCF (Edidin, et al 2010). Using Medicare claims data, 81,662 patients that had a vertebroplasty or kyphoplasty procedure had a higher survival rate at 24 months than non-operated patients: 74.8% versus 67.4% for non operated patients. Vertebral augmentation patients were 44% less likely to die than non-operated VCF patients (adjusted OR=0.56, $p<0.0001$). This data underscores that conservative treatment does indeed carry genuine risks to elderly patients, many of whom have other co-morbidities such as diabetes, COPD, or cardiovascular disease.

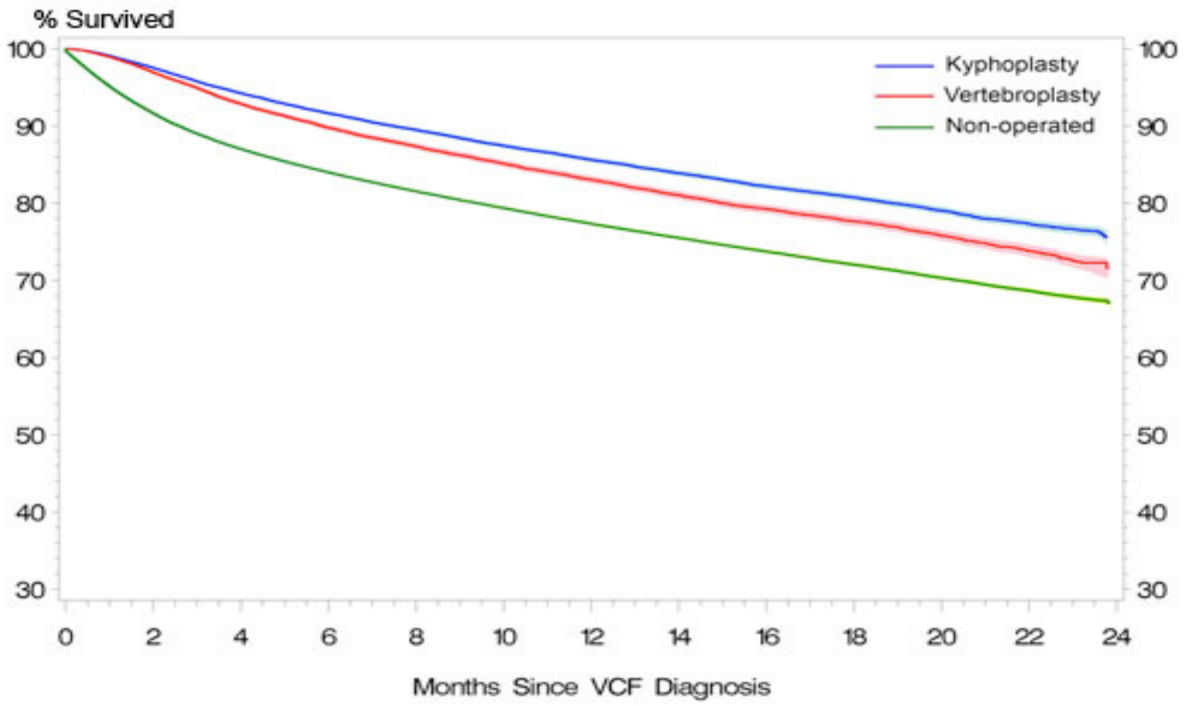


Fig. 1: Survivorship of non-operated VCF patients and VCF patients who underwent vertebroplasty or kyphoplasty between 2006 and 2007, following VCF diagnosis.

Edidin, et al 2010

SIR will be part of future trials of vertebroplasty that may confirm or contradict these studies or may identify subsets of patients more likely to benefit from vertebral augmentation. The SIR remains an active participant in trials, and we anticipate that spinal procedures will once again be highlighted at the SIR's Annual Scientific Meeting in March, 2011.

Summary

In our professional forums, and at our annual meetings, we take great care to ensure that the clinical training and symposia offered to our members reflect the highest standard of medical evidence and optimum patient care practices. The SIR's revised Position Statement will again emphasize the evidence-based course of care for VCF patients, to include a physical exam, imaging to confirm an acute/subacute fracture(s) with anatomy appropriate for vertebroplasty, patient documentation, explanation of risks, benefits, and alternatives to the patient and family, follow up care protocol including osteoporosis evaluation, and detailed post-procedure correspondence with the referring physician. The American College of Radiology guidelines are currently being updated as well and will have updated patient selection appropriateness criteria.

We recognize and encourage preoperative evaluation and management for all of these patients with appropriate physical examination and additional imaging studies as indicated to best define the clinical diagnosis of vertebral compression fractures. In the setting of fractures establishing

the diagnosis of osteoporosis, the treating physician will also coordinate with the primary provider to help initiate the work-up and treatment of osteoporosis consistent with National Osteoporosis Foundation (NOF) guidelines and PQRI. SIR also recognizes the interventional radiologist has the requisite clinical acumen to make appropriate treatment decisions in this set of patients. In our clinical opinion, SIR recommends that follow-up appointments should be scheduled either with the operating or referring physician by 2 weeks. The patient should be instructed to contact either physician sooner if other symptoms occur. Discussion with the patient and family should review other important symptoms including: Increased pain, extreme fever, numbness or tingling in limbs, and finally any neurologic complications, etc.

In sum, based on medical evidence, SIR considers percutaneous vertebroplasty or kyphoplasty as medically appropriate treatment when standard medical therapy has failed to relieve symptoms and any of the following criteria is met:

- osteoporotic, osteolytic, osteonecrotic (i.e., Kummell disease), or steroid-induced vertebral compression fracture(s) with persistent, debilitating pain unresponsive to conservative medical management. Clinical questions to consider with regard to timing intervention include the patient's ability to accomplish activities of daily living (ADLs), excessive pain requiring high or IV narcotic dosages, skilled care needs, occurrence of additional fracture, and the risk of further vertebral collapse

- back pain secondary to destruction of vertebral body due to osteolytic vertebral metastasis or multiple myeloma

- acute compression fractures so painful that hospitalization is required

- painful and/or aggressive hemangioma or eosinophilic granuloma of the spine

We believe that the scientific evidence supporting the continued payer coverage of vertebroplasty and kyphoplasty is strong, and that in our opinion, the procedures are cost-effective in that they allow many patients to recover at home, instead of a potential lengthy hospital stay. Many patients are benefiting from vertebral augmentation procedures every day and enjoying a more active lifestyle with fewer complications as a result of the procedures.

We thank you for the opportunity to express our opinion on the technology assessment. If the SIR can be of any assistance during your review, please do not hesitate to contact Tricia McClenny, Interim Executive Director at (703) 460-5565, or tmcclenny@sirweb.org.

October 22, 2010

Sincerely,

James F. Benenati, MD, FSIR
President
Society of Interventional Radiology
3975 Fair Ridge Drive, Suite 400 North
Fairfax, VA 22033

Robert Zeman, MD
Chair
American College of Radiology CAC Network
1891 Preston White Drive
Reston, VA 20191

Encl: 1) 2007 Position Statement on Percutaneous Vertebral Augmentation: A Consensus Statement Developed by the 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

2) November 24, 2009 Society of Interventional Radiology Commentary on Vertebroplasty and the August Studies in the New England Journal of Medicine

3) William Clark, M.D., St George Private Hospital, Sydney, Australia: "I was the Australian operator in Kallmes et al and regard the study as meaningless. I have conveyed this to Dr. Kallmes." http://www.arthritistoday.org/news/vertebroplasty-no-benefit.php (Arthritis Today, Sept. 5, 2009) (Link accessed 8/11/10)

4) October 2009 *Research Reporting Standards for Percutaneous Vertebral Augmentation: Society of Interventional Radiology.* J. Vasc. Interv Radiol 2009;20:1279-1286.

cc: Gerald Niedzwiecki, MD, FSIR, Chair, SIR Economics Committee
George Fueredi, MD, FSIR, SIR Health Policy and Economics Division Councilor
R. Torrance Andrews, MD, FSIR, SIR Clinical Practice Division Councilor
Michael Braun, MD, SIR CAC Workgroup Chair

October 22, 2010

Sean Tutton, MD, FSIR, SIR RUC Advisor
Tricia McClenny, SIR Interim Executive Director
Stephanie Le, ACR CAC Network Staff

NORTH AMERICAN SPINE SOCIETY
7075 Veterans Boulevard, Burr Ridge, IL 60527
Toll-free: (866) 960-6277 Phone: (630) 230-3600
Fax: (630) 230-3700 Web: www.spine.org

North American Spine Society
Newly Released Vertebroplasty RCTs: A Tale of Two Trials

Summary
On August 6, 2009, the *New England Journal of Medicine* published two randomized controlled trials on vertebroplasty: *A Randomized Trial of Vertebroplasty for Painful Osteoporotic Vertebral Fractures [1]* and *A Randomized Trial of Vertebroplasty for Osteoporotic Spinal Fractures [2]* . As the only multidisciplinary organization representing spine care providers, the North American Spine Society (NASS) has reviewed the studies and crafted the following comments on these important new studies and their significance to patient care.

A common initial reaction to the findings of these two prospective randomized controlled trials (PRCTs) has been surprise and even disbelief. A prominent, respected academician-surgeon who is an internationally respected leader in the field of osteoporosis research had described the procedure as "an opportunity to do something really good for patients [3]." Numerous large case series, both prospective and retrospective, had demonstrated very encouraging results with dramatic pain relief in appropriately selected patients. Even higher level data derived from a prospective comparative cohort study indicated a clear benefit over nonoperative treatment [4]. Moreover, for any physician who has performed vertebral augmentation procedures for osteoporotic compression fractures, experience has indicated that patients have dramatic pain relief, often within hours of the intervention. Some of the authors have personally seen these seemingly miraculous cases in which a bed-bound elderly person has had one or two vertebrae augmented after which they become nearly pain free and ambulatory. The evidence and experience up to the publication of the studies by Buchbinder et al. and Kallmes et al. have been overwhelmingly positive. Spine care providers are now, however, faced with a large chasm between these previous data and experiences and the latest, highest quality data.

The two PRCTs in question could be scrutinized. Like any attempt at comparing two treatments in a systematic and controlled manner, there are inevitably biases and factors that can favor one treatment over another. However, there is no such thing as an infallible PRCT. That being said, any group who undertakes such a task should be praised.

The intent of this analysis is not to in any way defame the studies or question the integrity of the authors. Instead, it is to perhaps help explore why there is such a seeming disconnect between the conclusions of these two PRCTs and previous experience and data. Without being overly critical and judgmental, there are a number of key factors that should be noticed.

Patient Selection

Fracture Acuity

The acuity of osteoporotic vertebral compression fractures (VCFs) has long been thought to influence the results of cement augmentation. Using a bone scan as a measure of fracture acuity, one study, of which Dr. Kallmes was a coauthor, concluded that "increased activity … is highly predictive of positive clinical response to percutaneous vertebroplasty [5]." While bone scans are no longer commonly used in the diagnostic evaluation of vertebral compression fractures, magnetic resonance imaging (MRI) scans are. Extrapolating from the scintigraphic data, it is generally believed that fracture edema, defined as increased signal on a fat-suppressed image or decreased signal on a T1-weighted image, noted on an MRI would be similarly predictive of a positive response to vertebral augmentation.

In fact, Buchbinder et al. utilized fracture edema or a fracture line detected on an MRI as part of the inclusion criteria. Buchbinder et al. further validated that "bone marrow edema indicates an acute fracture." However, by their description, a detectable fracture line sufficed for inclusion in the study. It is possible that the presence of a fracture line might indicate a cleft of nonunited bone, but it is unclear if this is a sign of an acute fracture. In contrast, Kallmes et al. utilized MRI or bone scan only in cases in which the fracture age was uncertain.

Both groups indicated that eligible patients had to have a fracture that was less than one year old. However, a fracture age of one year or less is not generally described as acute. In fact, most would define a maximum age of four to six weeks as the definition of an acute fracture [6, 7]. Thus, there appears to be some inconsistency between previous literature and the current studies in the description of a fracture as acute. Furthermore, it would seem that chronological age of the fracture is difficult to measure by radiographic means and would be more aptly "measured" by patient history (i.e., time elapsed since the pain started).

It should be noted that many of the patients in both the Buchbinder et al. and the Kallmes et al. studies had fractures that were less than six weeks old. In the former, 32 percent were less than six weeks old. In the latter study, 44 percent of fractures were one to fourteen weeks old. Admittedly, subgroup calculations did not demonstrate statistically significant differences between older and younger fractures with the available numbers.

Regarding fracture acuity, it is useful to consider a recently published, non-industry sponsored, non-randomized prospective double-cohort study that compared vertebroplasty to nonoperative treatment for VCFs [4]. While this study found statistically significant differences at three months follow-up, there was no difference at six months and one year follow-up. This study provides compelling evidence that pain from osteoporotic VCFs substantially diminishes over time. Furthermore, it would be reasonable to conclude that sometime between three months and six months fracture pain reduces to a level equivalent to the pain reduction that might be observed with vertebroplasty. Thus, the results of the Kallmes et al. and Buchbinder et al. studies are not surprising at all. The plurality of fractures was greater than three months old suggesting that fracture pain should have been substantially reduced. It is possible that this group was self-selecting as they may have been the most willing to be randomized to a so-called sham procedure.

Enrollment

Enrolling patients in a PRCT is a difficult task. Trying to explain to someone who is in excruciating pain that he or she will be assigned, at random, to either the group getting the new, promising procedure or to the group getting a sham injection is a difficult task. By the very nature of this conversation, many patients will not consent to the study, representing a selection bias. It is reasonable to think that patients in severe pain would more often opt to decline the study and proceed with vertebroplasty. It would have been useful to see the outcomes of this group of patients; similar to that published by Weinstein et al. in the recently published Spine Patient Outcomes Research Trial (SPORT) studies for lumbar degenerative disorders [8].

This pattern seemed to have been the case with the two studies in question. In the Kallmes et al. study, 1812 patients were initially screened, yet only 131 were entered into the study. The most common reason for not being entered into the study was patient refusal. Similarly, Buchbinder et al. required 4.5 years to accrue 78 patients at four high volume centers, reporting that 141 who satisfied all inclusion criteria declined randomization. The pain severity and functional compromise of the groups of patient who refused participation were not reported. Thus, there exists an unquantifiable selection bias in the final patient group.

Control Group

The control groups in both of these studies underwent supposed sham procedures. However, this was not so much a sham procedure as it was an alternative intervention. Injection of anesthetic into the facet capsule and/or periosteum may have had a plausible mechanism of pain relief in this patient population, albeit not fracture pain relief. While it is stated in both studies that patients had back pain, it is unclear if the origin of the back pain was the osteoporotic VCF or other common reasons for back pain in the elderly, such as arthritis facet pain. By nature of the patient population studied, “sham” facet injections may have led to decreased facet pain. Perhaps a sham procedure in which a dry needle was inserted might have been a more appropriate control.

Outcomes

In the Kallmes et al. study, the investigators stated that back pain was measured. However, there did not appear to be an effort to determine if reported back pain indeed originated from the osteoporotic fracture site. In the experience of some spine care providers, related to vertebral augmentation, it has been found useful to percuss or palpate the spinous processes systematically in order to find a level of maximal tenderness. This can then be marked with a radiographic marker to help localize the region of pain to a specific fractured vertebra. It is not uncommon for a patient to have pain that is distant from the fracture site, which would greatly diminish confidence that the perceived pain was originating from the fracture site. A bit more confusing was the assessment of “overall pain” in the Buchbinder study. It is unclear if this was an assessment of back pain or a more general measure of patients’ bodily pain.

Another important observation concerns the pain reduction observed in these two PRCTs. In the Kallmes et al. study, the authors reported an average reduction of three Visual Analog Scale (VAS) points at one month follow-up. In the Buchbinder et al. study, an average reduction of 2.3 was reported. In a recently published, industry-sponsored, PRCT comparing kyphoplasty (a comparable vertebral augmentation procedure to vertebroplasty) to nonoperative treatment, an average pain reduction of 3.5 VAS points was

reported [1]. The results of these three PRCTs do not appear to be dissimilar, notwithstanding other differences in the study.

A Look to the Future

Both groups of authors should be congratulated for undertaking the onerous task of performing high-level studies on an imminently important clinical disorder in our aging population. It is hoped that these data will help better define the indications for this potentially beneficial procedure. In addition, future PRCTs might benefit from a more strict mechanism by which patients with truly acute pain relatable to an osteoporotic VCF are enrolled. As both the Buchbinder et al. and Kallmes et al. study have taught us, this is likely to be a difficult task that may take a long period of time.

Conclusion

Beyond the lay press releases which claim "Vertebroplasty found to be useless for osteoporotic fracture and disc pain," [9] it is time for cooler heads to prevail. The medical literature thirsts for evidence. The data from these two studies must be considered carefully and thoughtfully. As discussed above, the findings of these investigations are not surprising and indeed not that dissimilar to previous data. The conclusions drawn by the authors, however, may not be as decisive as they appear. More practical conclusions should be made based on a thorough and systematic review of *all* the literature in order to better define the subgroup of patients for which vertebroplasty might be most appropriate.

On Behalf of the North American Spine Society

Christopher Bono, MD
Evidence-based Compilation & Analysis Director
Evidence-based Guideline Development Committee Chair

Michael Heggeness, MD, PhD
Former Research Council Director

Charles Mick, MD
Health Policy Council Director

Daniel Resnick, MD
Clinical Research Development Director

William C. Watters, III, MD
Research Council Director

Disclosures:

Christopher Bono, MD

Current
Royalties: Life Spine (Level B);
Consulting: Depuy Spine (Level B), Medtronic Sofamor Danek (Level B);
Speaking and/or Teaching Arrangements: Depuy Spine (Level C); Stryker Spine (Level B)
Boards of Directors: North American Spine Society
Other Offices: Applied Spine (Level B, Adverse Events Panel)
Research Support: Staff and/or materials: Archus Orthopedics (Level B); Synthes Spine (Level D)
Grants: Stryker Spine (Level D)
Fellowship Support: Depuy Spine (Level E)

Michael Heggeness, MD, PhD

Current
Royalties: Relievant Medsystems (Level C)
Stock Ownership: Relievant Medsystems (Level D)
Consulting: Relievant Medsystems (Level D 2008, None 2009)
Boards of Directors: North American Spine Society
Research Support: Investigator Salary: Department of Defense (Level E)
Grants: Department of Defense (Level I, not directly related to the spine)

Charles Mick, MD

Current
Boards of Directors: North American Spine Society

Relationships Outside the One Year Requirement
DePuy (Level A), Synthes (Level A), St Francis Medical (Level A) (Other [NASS Board, Coding Committee, Performance Measure Committee, Advocacy Council Chair, Annual Meeting, NASS RUC Rep]

Daniel Resnick, MD

Current
Boards of Directors: North American Spine Society

Relationships Beyond One Year Requirement
Medtronic (Consultant 2003-2006, minimal-less than Level B over entire duration)

William C. Watters, III, MD

Current
Consulting: Stryker (Level C)
Boards of Directors: North American Spine Society
Scientific Advisory Board: Intrinsic Therapeutics (Nonfinancial, Stock Options (No current value))
Others: Blackstone Medical Inc. (Financial, Clinical Events Committee for clinical trial)

Range Key:

Level A. $100 to $1,000

Level B. $1,001 to $10,000

Level C. $10,001 to $25,000

Level D. $25,001 to $50,000

Level E. $50,001 to $100,000

Level F. $100,001 to $500,000

Level G. $500,001 to $1M

Level H. $1,000,001 to $2.5M

Level I. Greater than $2.5M

1. Buchbinder R, Osborne RH, Ebeling PR, Wark JD, Mitchell P, Wriedt C, et al. *A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. N Engl J Med*. 2009. 361(6):557-568.
2. Kallmes DF, Comstock BA, Heagerty PJ, Turner JA, Wilson DJ, Diamond TH, et al. *A randomized trial of vertebroplasty for osteoporotic spinal fractures. N Engl J Med*. 2009. 361(6): 569-79.
3. Einhorn TA. *Vertebroplasty: an opportunity to do something really good for patients. Spine*. 2000. 25(9): 1051-1052.
4. Alvarez L, Alcaraz M, Pérez-Higueras A, Granizo JJ, de Miguel I, Rossi RE, et al.. *Percutaneous vertebroplasty: functional improvement in patients with osteoporotic compression fractures. Spine*. 2006. 31(10): 1113-8.
5. Maynard AS, Jensen ME, Schweickert PA, Marx WF, Short JG, Kallmes DF. *Value of bone scan imaging in predicting pain relief from percutaneous vertebroplasty in osteoporotic vertebral fractures. ANJR Am J Neuroradiol*. 2000. 21(10): 1807-12.
6. Ross PD, Ettinger B, Davis JW, Melton LJ 3rd, Wasnich RD. *Evaluation of adverse health outcomes associated with vertebral fractures. Osteoporosis Int*. 1991. 1(3): 134-140.
7. Gray DT, Hollingworth W, Onwudiwe N, Deyo RA, Jarvik JG. *Thoracic and lumbar vertebroplasties performed in US Medicare enrollees 2001-2005. JAMA*. 2007. 298(15): 1760-1762.
8. Weinstein JN, Lurie JD, Tosteson TD, Skinner JS, Hanscom B, Tosteson AN, et al. *Surgical vs. nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT) observational cohort. JAMA*. 2006. Nov 22;296(20):2451-2459.
9. http://www.beforeyoutakethatpill.com/index.php/2009/08/06/vertebroplasty-found-to-be-useless-for-osteoporotic-fracture-and-disk-pain/comment-page-1/.

To: Washington State Health Care Authorities

Date: October 20, 2010

Re: Washington Health Technology Assessment on Percutaneous Vertebroplasty, Kyphoplasty and Sacroplasty

Stryker is pleased for the opportunity to submit comments on the draft technology assessment on percutaneous vertebroplasty (PV), kyphoplasty and sacroplasty. We are a global leader in medical technology and offer products and services which span a broad range of medical specialties. Among these, are products used to perform PV and kyphoplasty. The Washington health technology assessment of these procedures primarily focuses on an analysis of the efficacy based on randomized studies and an analysis of the effectiveness based on nonrandomized observational studies. The results of this analysis suggest that the Health Technology Clinical Committee will consider both vertebroplasty and kyphoplasty investigational and shift the existing coverage guideline to one that precludes coverage. However, we feel strongly that such a shift from coverage to non-coverage for an accepted standard of care requires robust data *disproving* effectiveness in specific patient populations and this level of robust data does not exist. To the contrary, we believe that there is adequate evidence proving the effectiveness and benefit of both treatments. We, therefore, believe it is appropriate for the Health Technology Clinical Committee to consider this assessment in a manner similar to any other medical reference, integrating the information with all other pertinent information to allow physician providers to make decisions within the context of individual patient circumstances and resource availability.

Our comments are summarized below with more detailed discussion in the following sections.

In brief:

- In 2009, the publication of two sham controlled randomized studies of PV prompted many health policy makers to reconsider the existing positive coverage of PV and kyphoplasty.
    - While these randomized studies have been characterized as "negative," the Washington health technology assessment correctly concludes that these studies are merely inconclusive.
    - Therefore, there is no strong data to show that PV is ineffective.
- While sham controlled studies are considered the highest form of evidence, it has been extremely difficult to enroll adequate numbers of patients, as reflected in the small size and poor accrual to the recent studies.
    - This situation suggests that an evidence requirement calling for sham controlled studies is not feasible.
    - Sham controlled studies are also associated with a selection bias as patient enrollment is influenced by the design.
- The VERTOS II trial and the FREE study of kyphoplasty are unblinded, randomized studies comparing PV and kyphoplasty, respectively, to medical management.

    - These studies represent the best available data; however, the technology assessment devalued these positive results due to the absence of a sham control.
- Given that PV and kyphoplasty are considered standards of care, it is appropriate to consider the overall weight of the evidence, including data from retrospective and prospective case series that consistently reports the clinical benefit of the two procedures.
    - All of the private payers cited in the technology assessment consider PV and kyphoplasty as medically necessary based on this weight of the evidence.
        - These policies reviewed the two sham controlled trials and noted the data is inadequate to reverse the existing coverage policies.
- Based on these considerations, we encourage the Health Technology Clinical Committee to recommend continued coverage for PV and kyphoplasty thus ensuring patients of Washington state agencies continued access to these procedures.

Sham Controlled Randomized Studies

As noted in the technology assessment, two recently published sham controlled randomized studies of percutaneous vertebroplasty (Buchbinder 2009, Kallmes 2009) "did not have adequate power to detect differences in the proportion of patients with clinically meaningful improvement." The inability to enroll large number of patients in a sham controlled study is a common problem for all surgical procedures, particularly for percutaneous vertebroplasty, which is considered a standard of care by many physicians.

While randomized controlled trials are considered the highest form of evidence, the biases inherent in recruiting patients into a sham controlled randomized study must be recognized. Patients in acute or subacute pain would be unlikely to enroll in a trial without an active treatment arm. However, these are the patients who may be the most likely to benefit from percutaneous vertebroplasty, as noted in a commentary by the National Association of Spine Surgeons (NASS) and in letters to the editor in the New England Journal of Medicine. Therefore, not surprisingly, the majority of patients enrolled in these trials had chronic pain, a patient group less likely to benefit from percutaneous vertebroplasty.

The only conclusion that can be drawn from these two sham studies is that the randomized studies were inadequately powered to show a treatment effect, a conclusion which is correctly stated in the technology assessment. *However, it is important to note the lack of data does not mean that there is a lack of benefit. Instead, the randomized studies reflect the difficultly of performing sham controlled studies of an accepted standard of care.*

Unblinded Randomized Studies

The technology assessment also reviews the recently published VERTOS II study (Klazen 2010), a randomized study comparing PV with continued medical management. This study is the only randomized study of PV that has enrolled patients with acute osteoporotic fractures. As noted in the technology assessment, this study "demonstrated

statistically significant improvement in pain scores that was sustained to the 12 month follow up."

The technology assessment correctly notes the "extent to which lack of patient blinding and possible placebo effect may contribute to the findings is not clear," reflecting the lack of a sham control. However, given the extreme difficulty in enrolling patients to a sham controlled trial, the VERTOS II study represents the highest quality data regarding PV for acute fractures. Part of the strength of this study is the persistent benefit at the 1 year follow up*, which would surpass the duration of any possible placebo effect*. In addition to long term pain relief, this study demonstrated a very rapid pain relief; this short term outcome is very important in and of itself because patients with debilitating acute pain are not candidates for long term conservative therapy. Essentially, prompt relief of pain is one of the most basic principles of medicine.

It is certainly true that a sham-controlled trial provides the highest quality data, but alternative data, such as the VERTOS II study should not be dismissed because it does not meet an unrealistic standard. In addition, the technology assessment included three other studies that consistently reported that percutaneous vertebroplasty was associated with improved pain relief compared to conservative medical management.

The technology assessment also reviewed a large randomized trial (the FREE study) comparing kyphoplasty to medical management in 300 patients with acute osteoporotic vertebral fractures. (Wardlaw 2009) Compared to the control group, the balloon kyphoplasty patients showed:

- Greater improvement in SF-36 physical component summary score at one month that was maintained on average over the 12-month period.
- More improvement in back function as measured by the *Roland-Morris Back Function Scale* at one month and at 12 months. Additionally, they reported fewer days of limited activity due to back pain and less walking aid usage over the 12-month period.
- Less back pain and reduced usage of analgesics over the 12-month period.

Regarding this trial, the technology assessment noted "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 estimated may change with additional research."

This conclusion of the technology assessment implies that multiple randomized trials are needed. The FREE study was a large RCT of 300 patients performed in 21 institutions. While confirmatory studies may be appropriate for small randomized trials, the large size and multiple institutions participating in the FREE study mitigates the need for multiple confirmatory studies. Additionally, the assessment cites two additional non-randomized studies that consistently reported improved pain relief associated with kyphoplasty.

The Weight of the Evidence

The study selection criteria of the technology assessment were limited to studies that compared vertebroplasty or kyphoplasty with a comparison group using a randomized controlled trial or cohort study design. As noted above, randomized controlled trials of standards of care are difficult if not impossible to conduct and the technology assessment concluded that the absence of a sham control makes limits any possible conclusions. These parameters essentially guaranteed the literature would be considered inadequate.

In this situation, it is important to consider the weight of the evidence from the overall body of literature. The assessment did consider systematic reviews, which included a broader selection of studies, but only in the context of safety. In general, these studies published by a number of institutions within and outside the United States have consistently reported favorable outcomes for both PV and kyphoplasty. A summary of the efficacy outcomes in these studies can be found in Tables 6 and 7 in the 2010 Blue Cross Blue Shield Association Technology Assessment.

It is evident that payers have considered the positive weight of the evidence in the development of their existing coverage policies. All of payer coverage policies cited in the technology assessment state that PV and kyphoplasty are considered medically necessary, i.e. not investigational. Many of these policies note the absence of high quality clinical trials but point to the consistent results of prospective and retrospective cases series, studies that were excluded from the Washington health technology assessment. In addition, many of these payers reviewed the two sham controlled studies of percutaneous vertebroplasty published in 2009 (Kallmes 2009, Buchbinder 2009) and concluded that the inconclusive results of these studies are inadequate to overturn the existing positive coverage policy. The Anthem medical policy provides a representative sample:

> "Evidence regarding efficacy of percutaneous vertebroplasty (PV) comes from a number of prospective, uncontrolled trials, case series reports, and several retrospective studies. Two large case series (total of 421 participants) indicated percutaneous vertebroplasty (PV) was highly effective in significantly reducing pain and increasing mobility in over 70% of individuals with vertebral body lesions with minimal complications. Additionally, a number of smaller prospective, uncontrolled studies and several retrospective studies (total of 564 participants) all reported that PV significantly reduced pain and improved mobility in the majority of participants, with few individuals experiencing persistent mild pain. Results from the majority of these studies indicate PV can produce significant pain relief, increase mobility, and improve quality of life in 70% to 80% of individuals with osteolytic lesions from hemangiomas, metastases or myeloma, or osteoporotic compression fractures. In these studies, pain relief was apparent within 1 to 2 days after injection and persisted for at least several months and up to several years. Complications were relatively rare with a higher rate in individuals with malignant processes, due primarily to leakage of cement from extensive lytic regions in the vertebral bodies and to the poor overall health status of these individuals.

> …Given the subjective outcome of pain, a placebo effect is expected with both vertebroplasty and kyphoplasty. Therefore, a placebo-controlled randomized controlled trial would ideally confirm that the treatment effect surpasses the placebo effect. Although such a study has not been done, the reported cases series from multiple different institutions have consistently reported statistically significant reductions in pain compared to baseline. When long term results are reported, the treatment effect appears to be durable. Based on this data, both kyphoplasty and vertebroplasty have emerged as an accepted option for those with vertebral lesions that have not responded to conservative therapy. However, individuals who undergo either procedure should be informed of a significant risk of subsequent spinal fracture. Whether this risk is greater than the natural history of the treated condition as a result of the procedure is not known."

In summary, we respect the thorough technology assessment commissioned by the Washington State Health Care Authority, but contend that as a standard of care, any assessment of PV or kyphoplasty must consider the overall weight of the evidence rather than invoking an evidencs standard of sham controlled randomized studies which, based on the poor enrollment of such studies, has been shown to not be feasible. A preponderance of private payers have considered the weight of the evidence, which includes the large number of retrospective and prospective cases that have consistently reported positive results, and concluded that percutaneous vertebroplasty and kyphoplasty are medically necessary and not investigational.

We thank you for the consideration of our comments on this topic.

Sincerely,

Dr. Rodney Parker
Sr. Regulatory Affairs Manager, Clinical Affairs
Stryker Instruments

References:

Anthem Medical Policy: Percutaneous spinal procedures: Vertebroplasty, kyphoplasty, sacroplasty. Available at: http://www.anthem.com/ca/medicalpolicies/policies/mp_pw_a050268.htm

Blue Cross Blue Shield Association Technology Evaluation Center. Percutaneous vertebroplasty or kyphoplasty for vertebral fractures caused by osteoporosis. Available at: http://www.bcbs.com/blueresources/tec/vols/24/percutaneous-vertebroplasty.html

Buchbinder R et al. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. N Eng J Med 2009;361:557-568.

Kallmes DF et al. A randomized trial of vertebroplasty for osteoporotic spinal fractures. N Eng J Med 2009;361:569-79.

Klazen CAH, Lohle PNM, de Vries J et al. Vertebroplasty versus conservative treatment in acute osteoporotic vertebral compression fractures (VERTOS-II): An open label randomized trial. Epub ahead of print: August 10, 2010.

Letters to the Editor. Trials of vertebroplasty for vertebral fractures. N Eng J Med 2009;361:2097-2100.

North American Spine Society: Newly released vertebroplasty RCTs: A tale of two trials. http://www.spine.org/Documents/NASSComment_on_Vertebroplasty.pdf

Wardlaw W, Cummings SR, Van Meirhaeghe J, et al. Efficacy and safety of balloon kyphoplasty compared with non-surgical care for vertebral compression fracture (FREE): a randomised controlled trial. Lancet. 2009; Vol 373. Published on www.thelancet.com on February 24, 2009.

Appendix A
NASS comment

Evidence of the Clinical Effectiveness and Safety of Kyphoplasty in the Treatment of Vertebral Compression Fractures

Medtronic, Inc. Response to the
State of Washington Health Care Authority
Health Technology Assessment
On Vertebroplasty, Kyphoplasty and Sacroplasty

October 20, 2010

TABLE OF CONTENTS

1. PURPOSE

The purpose of this document is to provide the Washington State Health Care Authority with additional evidence demonstrating the clinical effectiveness, safety, and coverage of kyphoplasty in the treatment of vertebral compression fractures (VCFs) that were not included in the Health Technology Assessment (HTA) dated October, 7, 2010. In addition, corrections to certain mischaracterizations that appear within the HTA are submitted for consideration.

In addition, three appendices are referenced that contain supplemental material as described below:

1. Appendix 1 lists and summarizes the 97 peer reviewed publications reporting original data on the treatment outcomes of cohorts of 10 or more patients treated with kyphoplasty based on a literature search conducted April 5, 2010
2. Appendix 2 reviews the safety of kyphoplasty and compares it to a different procedure, vertebroplasty
3. Appendix 3 contains information on existing health technology assessments (HTAs), national payer coverage policies, and CMS local coverage decisions (LCDs) that were not addressed by the Washington State Health Care Authority HTA and submits corrections to information that was mischaracterized.

2. Vertebral Compression Fractures – Increased Deformity, Morbidity and Mortality

The presence of vertebral deformities and/or kyphosis has been shown in multiple studies published in the last two decades to profoundly impact the health, quality of life, and survival of patients with VCF. All of these studies were performed on patients who were medically stable but showed evidence of vertebral deformity on plain film X-ray, and/or had measurable kyphosis.

Osteoporotic spinal deformity alone is associated with severe health consequences – reduced pulmonary function, reduced physical function, appetite loss resulting in physical frailty, gait alterations that impair mobility and balance, chronic back pain related to facet tension and/or paraspinal muscle fatigue associated with compensatory posture, loss of quality of life, increased risk of future fracture, and decreased survival.[1,2,3] These effects are related to the severity of the spinal deformity and are independent of acute fracture pain.[4]

Table 1	
Clinical Study Documented Health Effects of VCF Related Deformity	
1.	Even one deformed vertebral body detected radiographically reduces physical function in elderly women.[5]
2.	Patients experience a 9% reduction in forced vital capacity for each thoracic prevalent VCF.[6]
3.	Patients with 3 or more prevalent VCFs lose quality of life similar to patients with cardiac disease, peripheral disease, and diabetes mellitus.[7]
4.	Vertebral compression fracture excess mortality is similar to that of hip fracture.[8]
5.	Community-dwelling elderly subjects with spinal hyperkyphosis were 50% more likely to die within four years than the population in general.[9]
6.	VCFs beget more VCFs – future fracture risk roughly doubles with every two prevalent (chronic) fractures.[10]

These documented effects are also predicted by spinal biomechanics. The collapse of the anterior spine decreases patient height and tilts the patient's trunk forward, increasing the forward bending moment on the front of the spine. This increases anterior loads, predicting increased fracture risk with increasing deformity. It also reduces thoracic space, affecting pulmonary function, and decreases abdominal space, reducing appetite. Hamstring foreshortening leads to the altered gait and mobility loss.[11] Sources of chronic back pain include paraspinal muscle firing to maintain a compensatory stance for upright posture and/or tension on the facets due to abnormal forward curves, as well as rib-on-pelvis pain in severe deformity.[12]

All of the effects of uncorrected vertebral deformity predicted by the biomechanics of the spine have been documented in osteoporotic patients with prevalent VCFs and/or spinal deformity in the absence of acute back pain. Table 2 provides the mechanism for the sequelae observed in patients who undergo non-surgical management, resulting in spinal deformity.[12]

Table 2	
Mechanical Effect of VCF	**Predicted Clinical Consequences**
↓ Thoracic space	↓ Pulmonary function
↓ Abdominal space	↓ Appetite → ↑frailty, ↑ GI effects
↑ Force on anterior vert. body	↑ Future VCF risk
Center of gravity shifts anterior	Forward force → compensatory stance to stand upright
Kyphosis, compensatory stance	Hamstring foreshortening → ↓ Gait velocity, distance → ↓ Mobility Paraspinal muscle firing to maintain stance → Chronic back pain

This large literature, developed over the last three decades, strongly supports the need for deformity correction. The profound clinical impact of VCFs treated with nonsurgical management, and the downward spiral of afflicted patients, are also described below, presented through the eyes of health care givers who treat patients with, and study the impact of, osteoporotic spinal deformity:

"The greater the deformity, the greater the likelihood of pain and disability. As height is lost, patients experience discomfort from the rib cage pressing downward on the pelvis. Patients develop a thoracic kyphosis, a lumbar lordosis, and a protuberant abdomen with prominent horizontal skin creases. The reduced thoracic space may result in decreased exercise tolerance and reduced abdominal space may give rise to early satiety and weight loss. Sleep disorders may occur. Patients lose self-esteem. Self care may become difficult. They are often depressed. They become fearful of future fracture. They have distorted body image and poor health perception. Patients with one vertebral fracture are at increased risk of peripheral fracture and further vertebral fracture." (p.S27)[13]

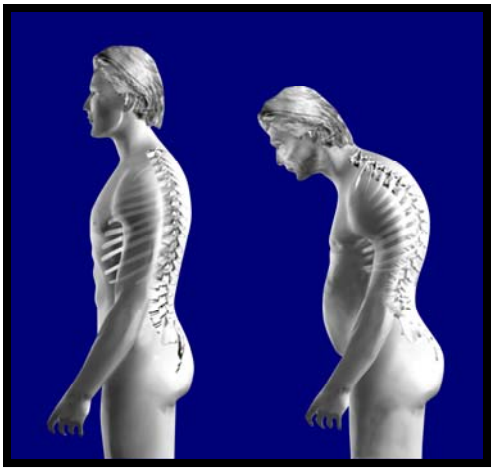


Figure 1 – Spinal Deformity Resulting From Vertebral Compression Fracture

This description is consistent with the additional observation that:
"Patients who suffer clinical vertebral fractures experience an abrupt descent into disease and disability."(p. 867).[14]

3. Kyphoplasty is Far More Than A Modification of Vertebroplasty

There are important differences between vertebroplasty and kyphoplasty that go beyond the HTA's portrayal of kyphoplasty as "*a modification of vertebroplasty that expands the partially collapsed vertebral body with an inflatable balloon before the injection of bone cement*". Key characteristics of the kyphoplasty procedure and their importance in the treatment of vertebral compression fractures (VCFs) are discussed in Figure 2 below:

(1) The bipedicular introduction of cannulae through two 1-cm incisions (also see Figure 2) into the fractured vertebral body under image guidance.

(2) The insertion of an inflatable bone tamp to elevate the vertebral body endplates and reduce spinal deformity. The inflation of the bone tamp compacts the cancellous bone, fills fracture lines and creates a void within the vertebral body.

(3-4) The controlled filling of the void with high viscosity bone cement under low pressure to distribute the cement across the vertebral body for reliable fracture stabilization. The advantages of void creation are a defined location with a known volume for cement placement along with the reduced potential for the fixation material to extend beyond the region of its intended application.[15]

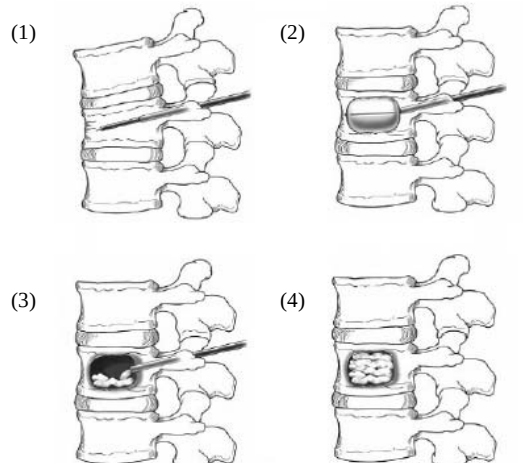


Figure 2 – Kyphoplasty stabilizes the fracture to alleviate pain and reduces the fracture to correct spinal deformity

The role of the void in kyphoplasty is critical to bone cement control and distribution. The lack of a void during vertebroplasty means that the practitioner must force bone cement into crushed bone. This is why vertebroplasty requires relatively liquid bone cement and higher injection pressures compared with kyphoplasty. Balloon inflation during kyphoplasty packs bone into fracture lines and disrupts the internal venous plexus, reducing leak pathways, as demonstrated by Phillips *et al*.[16] This creates an environment in which leaks are less likely to occur through fractures in the vertebral cortex or injection into the vertebral venous system. In order to minimize the risk of cement extravasation, vertebroplasty practitioners attempt to stop further cement injection once it is evident that cement has passed outside the vertebra. Nevertheless, cement leakage can still occur due to the surgeon's reaction time between visualization of the cement leak and cessation of the injection. Premature cessation of cement injection can also lead to inadequate cement filling of the fractured vertebra.[16]

3.1 The differences between kyphoplasty and vertebroplasty in the clinical literature have been recognized by the Technology Assessment Committee of the Society for Interventional Radiology:

> *"The most significant differences between the two procedures is the restoration of vertebral body height, thus reducing kyphosis at the treated level; and the associated long-term complications. Another potential benefit to kyphoplasty is the lower reported rate of cement extrusion. It has been shown that kyphoplasty may seal osseuous defects and venous pathways, thereby preventing cement from leaking."*[17]

3.2 The increased rate of cement leaks documented with the vertebroplasty technique compared to kyphoplasty predicts a higher rate of cement-related complications as well. This includes nerve root injury from foraminal leaks, cord/cauda equina compression from epidural leaks, as well as pulmonary emboli from venous leaks. While only large RCTs directly comparing the two procedures can definitely demonstrate safety differences, systematic literature reviews analyzing cement leaks and adverse events support this hypothesis.

- In the most recent meta-analysis comparing the incidence of complications in VCF patients treated with kyphoplasty (n=2,794 levels treated) vs. vertebroplasty (n=7,184 levels treated), Lee and colleagues found that vertebroplasty had a significantly higher rate of both total cement leaks (43% vs. 8.8%, $p<0.001$) and symptomatic cement leaks (1.08% vs. 0.04%, $p<0.001$) than kyphoplasty.[18]

- This result is consistent with previous formal analyses, documenting a higher pooled risk of pulmonary and neurologic complications during vertebroplasty than kyphoplasty.[19,20]

3.3 After compilation of the Washington State Health Care Authority's HTA, , the American Academy of Orthopaedic Surgeons released its *"Guidelines and Evidence Report on the Treatment of Symptomatic Osteoporotic Spinal Compression Fracture"* – it can be downloaded from the AAOS website at: http://www.aaos.org/Research/guidelines/SCFguideline.pdf.

The AAOS made the following recommendation in these guidelines:

> *"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."*

It should be noted that kyphoplasty is the ONLY therapy for the treatment and reduction of vertebral compression fractures recommended by the AAOS in this just released guideline.

4. Kyphoplasty – Correction of HTA Mischaracterization

The HTA stated that "*Kyphoplasty almost always requires general anesthesia and at least one overnight stay in the hospital*" (p28).

In fact, kyphoplasty can be done under local or general anesthesia and on either an inpatient or an outpatient basis[21] depending on the medical need of the patient as determined by the treating physician.[22],[23]

4.1 For example, Chung et al.[24] have reported on their VCF patient outcomes following treatment with kyphoplasty in which only local anesthesia was utilized while Wardlaw et al.[25] report results using general anesthesia for most patients.

4.2 Based on CMS MEDPAR data for calendar year 2009, approximately one-half of all kyphoplasty procedures are done on an inpatient basis, one-half are performed on an outpatient basis.[26]

5. The randomized controlled Cancer Fracture Evaluation (CAFE) Trial results should additionally be considered by the Washington State Health Care Authority in its assessment of kyphoplasty.

The Washington State Health Care Authority HTA considered the Fracture Reduction Evaluation (FREE) trial in its assessment of kyphoplasty. FREE is a randomized controlled trial comparing kyphoplasty to nonsurgical management (NSM) in the treatment of osteoporotic vertebral compression fractures (VCFs). Patients treated with kyphoplasty were found to experience statistically significant improvements in their quality of life and mobility and statistically significant reductions in their disability, pain and narcotic pain medication compared to patients in the NSM control group.[25]

In addition to FREE, the randomized controlled Cancer Fracture Evaluation (CAFE) trial has been completed and the results on its primary endpoint have been posted on the FDA/NIH www.clinicaltrials.gov website; reported at the 2009 American Society of Hematology Annual Meeting and posted on its website, http://ash.confex.com/ash/2009/webprogram/Paper24340.html; and published in abstract form in a journal supplement to Blood.[27]

In CAFE, 134 adult patients from 21 sites diagnosed with a variety of cancers and 1 to 3 painful VCFs (VAS $\geq$ 4) were randomly assigned. The primary outcome of the study was the one-month difference between groups in change from disability baseline scores using the Roland-Morris Disability Questionnaire (RMDQ). The RMDQ is a 0- (no disability) to 24-point (maximum disability) instrument validated for assessing back-specific physical functioning. Secondary measurements included back function and pain, quality of life, change in ambulation, pain medications and daily activities at baseline, and 1, 3, 6 and 12 months. Patients were randomized to kyphoplasty (N=70) or nonsurgical management (N=64), had an average age of 64 years, and 58% were female. Patients had multiple myeloma (38%), cancer of the breast (22%) or other cancers.

- RMDQ disability scores at pretreatment baseline were similar between the kyphoplasty (17.6) and nonsurgical management (18.2).
- At one month, there was an improvement for patients randomized to kyphoplasty of -8.3 points whereas those receiving nonsurgical management showed no significant change (0.1 points). The difference between the two groups was statistically significant, $p<0.0001$.
- At one month, the kyphoplasty patients also showed significant improvement in their back pain (-3.8) whereas the nonsurgical management control group patients experienced no significant change (-0.3). The difference between the two groups was statistically significant, $p<0.0001$.
- For kyphoplasty patients, the improvements in back pain and disability were sustained throughout the 12-month study period.
- Adverse events were similar between the two groups.
- One serious adverse event in the form of an intra-operative non-Q-wave myocardial infarction resolved and was attributed to anesthesia. One patient with a cement leakage to the disc had an adjacent fracture occur 1 day after the index procedure; the local investigator judged this to be device-related. However, at 1-month there was no difference in the number of patients with new radiographic or clinical fractures.

The CAFE authors concluded that cancer patients with VCFs treated with kyphoplasty had superior outcomes compared to those treated with nonsurgical management as measured by the primary endpoint and, as measured by other pain, and quality of life assessments; the results support the benefits of kyphoplasty in the management of cancer patients with VCFs.

Medtronic believes that the findings of the CAFE randomized controlled trial, in addition to those of FREE, should be thoroughly considered by the Washington State Health Care Authority in its assessment of kyphoplasty.

6. Prospective non-randomized comparative studies that have been published in peer-reviewed journals and should additionally be considered by the Washington State Health Care Authority in its assessment of kyphoplasty are noted below:

6.1 Kumar et al.[28] reported on a prospective study comparing patients with osteoporotic VCFs treated with either vertebroplasty (n = 28) or kyphoplasty (n=24). Patients in both groups experienced a statistically significant reduction in pain as measured by the visual analogue scale (VAS), a statistically significant reduction in disability as measured by the Oswestry Disability Index (ODI), and a statistically significant improvement in quality of life based on the Euroquol-5D (EQ_5D) and Short-Form 36 Health Survey (SF-36). At last follow-up (mean = 42 weeks), patients in the kyphoplasty group experienced statistically significantly greater improvements in VAS, ODI, EQ-D, and physical component dimensions of the SF-36 than did patients treated with vertebroplasty.

6.2 Komp et al[29] prospectively evaluated patients with radiologically verified osteoporotic VCFs who chose to be treated either with kyphoplasty (n=21) or nonsurgical management (n=19) and followed them for 6 months. The investigators found statistically significant improvement ($p<0.05$) in VAS pain and ODI disability scores at the 1-week, 6-week and 6-month follow-up in the kyphoplasty treatment group but no significant improvement in the nonsurgical management control group.

6.3 Dong et al.[30] measured thoracic kyphotic angle, local kyphotic angle, pain scores and pulmonary function parameters in 38 older women with osteoporotic VCFs before, three days after and three months after operation with kyphoplasty (n=20) or vertebroplasty (n=18).

- Vital capacity, forced vital capacity and maximum voluntary ventilation significantly increased three days after operation ($P < 0.01$), while maximum voluntary ventilation went on to improve three months later ($P < 0.01$)
- Thoracic kyphotic angle had a significant ($p<0.001$) negative correlation with vital capacity. That is to say, the greater the thoracic deformity, the greater the loss of the lung's vital capacity

- Patients treated with kyphoplasty achieved significantly greater vertebral body height restoration and correction of local kyphotic angle than those treated with vertebroplasty ($p<0.01$) at each follow-up.
- In the thoracic subgroups, improvement of the local kyphotic angle was significantly correlated with increased lung vital capacity and kyphoplasty was found to increase vital capacity significantly more than vertebroplasty ($P < 0.01$)

7. The Body of Clinical Evidence for kyphoplasty is consistent with the findings of the FREE and CAFE Randomized Controlled Trials

The results of the FREE and CAFE randomized controlled trials are consistent with the findings of a recent comprehensive review of the clinical literature. Based on a search of the U.S. National Library of Medicine database conducted on April 5, 2010, there have been a total of 97 publications (containing cohorts of 10 or more patients) in which 12,194 patients were enrolled. The search criteria employed, a summary of each paper, and a bibliography providing full citations for each publication is provided in Appendix 1. The published studies are noteworthy in that they uniformly show consistently positive results for VCF patients treated with kyphoplasty – see Table 3 below.

Table 3

Summary of Journal Publications on the Use of Kyphoplasty in the Treatment of Vertebral Compression Fractures

Endpoint	# of Studies Reporting on this Endpoint	# of Studies with Positive Kyphoplasty Results
Pain (NRS, VAS, others)	82	82
Ambulation, Activities of Daily Living	37	37
Disability (ODI, RMDQ)	30	30
Quality of Life Health Survey	13	13
Vertebral Height Restoration	58	60
Angular Deformity Correction	58	58

Based on a U.S. National Library of Medicine Literature Search as of April 05, 2010. See Appendix 1.

8. Peer-reviewed journal publications reporting findings of analyses of the National Inpatient Sample on individuals with vertebral compression fractures that should additionally be considered by the Washington State Health Care Authority in its assessment of kyphoplasty are noted below:

Background[31]:
The Nationwide Inpatient Sample (NIS) is one in a family of databases and software tools developed as part of the Healthcare Cost and Utilization Project (HCUP). A Federal-State-Industry partnership sponsored by the Agency for Healthcare Research and Quality, HCUP data inform decision making at the national, State, and community levels. NIS data are used by a variety of non-profit and for-profit organizations, including:

- Actuarial firms
- Accrediting bodies
- State and Federal Government agencies
- Health care consultants
- Health professions societies
- Health services researchers and policy analysts
- Hospital information system firms
- Hospitals and health care systems

- Health and life insurance companies
- Investment firms
- Managed care organizations
- Pharmaceutical and medical product manufacturers and marketing firms
- Schools of business
- Schools of public health
- Utilization review organizations.

NIS comparative data on the treatment of VCFs has been reported in two peer-reviewed journals.

8.1 Lad et al.[32] evaluated the 2004 NIS database to assess differences in the utilization and outcomes of vertebroplasty and kyphoplasty – each appearing for the first time under separate ICD-9 codes. The investigators reported that of the 23, 691 hospital inpatients with VCFs who were treated with either kyphoplasty or vertebroplasty, that those patients treated with kyphoplasty were more likely to have a shorter length of stay and were more likely to be discharged to their home (vs. an institution) than patients treated with vertebroplasty, while average hospital charges were similar. See data in Table 4 below.

Table 4

Total Inpatient Admissions for Vertebroplasty and Kyphoplasty in 2004 In the NIS database = 23, 691	Kyphoplasty (57%)	Vertebroplasty (43%)
% discharged to home	77%	50%
% discharged to institution	23%	50%
Length of Hospital Stay	3.7 days	7.3 days
Mean Hospital Charges	$30,144	$29,517

8.2 Zampini et al.[33] analyzed the 2005 NIS database to determine if differences existed in the outcomes of 5,766 patients admitted to the hospital via the emergency department due to painful VCFs based whether they were treated with kyphoplasty (15%) or with nonsurgical management (85%).

The investigators found that:

- VCF patients in the kyphoplasty and nonsurgical management groups had similar co-morbidity profiles.
- No significant between group differences existed in the overall rate of VCF patient complications
- Accelerating their return to function, VCF patients treated with kyphoplasty were found to be:
  - 2.59 times more likely to be discharged to their homes than patients treated with nonsurgical management (odds ration 2.59; $p<0.001$)
  - 38% less likely to be discharged to a skilled nursing facility than VCF patients treated with nonsurgical management (odds ratio 0.62, $p<0.001$)
  - 48% less likely to experience in-hospital mortality than VCF patients treated with nonsurgical management (odds ratio = 0.52, $p=0.003$)
- Kyphoplasty treated patients were found to have a longer length of hospital stay (0.7 day) and higher hospital charges than patients treated nonsurgically

The authors concluded that kyphoplasty for the treatment of VCFs may accelerate the return to independent patient function and that the initially higher cost of treatment may be offset by the reduced use of medical resources after hospital discharge.

9. A recently published abstract of a U.S. Medicare Based VCF survivorship study reports that kyphoplasty is associated with reduced mortality compared to nonsurgical management and vertebroplasty and should additionally be considered by the Washington State Health Care Authority in its assessment of kyphoplasty.

9.1 Previous researchers have shown that onset of a VCF compression fracture is associated with increased mortality, presumably both due to the direct effects of the VCF (immobility and nutritional changes) and to a VCF being a general marker of poorer health.[34] Since about the year 2000 surgical interventions, vertebroplasty (VP) and kyphoplasty (BKP) have been available in the U.S. market. Specific CPT codes delineating each procedure have been available since 2001; unique ICD-9 codes were introduced in Q4 2004.

Scientists at Drexel University, Exponent and Medtronic used the 100% Inpatient and Outpatient Medicare dataset obtained for the years 2005 to 2007 to estimate the survivorship of patients diagnosed with a VCF (ICD-9-CM 733.13, and 805.0,2,4,6 or 8).[35] Patients diagnosed during this time period could have been managed nonsurgically, or been treated with VP or BKP. Survivorship was compared at up to two years follow-up using Cox regression adjusted by a selected set of common comorbidities to account for incoming health status. In an attempt to primarily follow the course of index fractures, patients included in the overall dataset could not have had a VCF in the twelve months prior to diagnosis. The robustness of this assumption was subsequently tested using a two-year window and no measurable changes were observed.

Kaplan-Meier survivorship curves and adjusted odds ratios were used to compare 1) surgical intervention (BKP or VP) vs. nonsurgical management (NSM) and 2) BKP vs. VP vs. NSM. The Medicare denominator file was used to determine survivorship through the study period. The overall study included 410,965 patients divided into 53,820 kyphoplasty (KP) patients, 27,842 vertebroplasty (VP) patients, and 329,303 nonsurgically managed (NSM) patients.

At up to 24 months follow-up, patients that underwent surgical intervention had a higher survival rate of 74.8% compared to 67.4% for NSM patients ($p<0.0001$). VP or KP patients were 44% less likely to die by the end of the study than NSM patients (adjusted hazard ratio, HR = 0.56, $p<0.0001$). Furthermore, the survival rates for VCF patients followed VP or KP were 72.3% and 76.2% respectively. Overall, the risk of mortality was 12.5% lower for KP patients than for VP patients (adjusted HR=0.87, $p<0.0001$).

The data from this study strongly suggest that surgical intervention following a VCF diagnosis is warranted and valuable to the patient when mortality is used as the outcome metric. These data also suggest that the KP intervention is advantageous over the VP procedure although both have value over NSM.

The survival advantage with kyphoplasty (whose goal is to correct anatomy where possible) compared to vertebroplasty (which does not have a goal of anatomy restoration) is predicted by the poorer outcomes of elderly patients with vertebral deformities, including excess pulmonary deaths described by Kado et al.[36]

9.2 ***Embargoed confidential data follow. Not to be reproduced or transmitted in any form***[37]***.***
Subsequent to the two-year analysis, the authors performed a four-year analysis using the same methodology and covering the years 2004-2008. These data are still preliminary, but indicate two overall trends. First, the difference between patients undergoing surgical treatment vs. those not receiving surgical intervention continues to be statistically significant and in the favor of intervention at up to four years follow-up. Second, the difference between the intervention and non-intervention has widened such that at up to four years follow-up, BKP patients were 35% less likely to die by the end of the study, whereas VP patients were only 25% less likely to die on an adjusted hazard ratio basis. Alternatively stated, the overall risk of mortality was 17% lower for BKP patients than for VP patients (adjusted HR= 0.83, $p<0.0001$). ***These four-year data are preliminary and strictly under embargo as a full manuscript is under preparation for submission to a major medical journal in the next few weeks.***

In addition to carrying out the mortality analysis to four years, the research team has also performed a life-expectancy analysis using the Medicare data (Parts A & B, 5% cull) as the input to a Weibull model. While still preliminary, the initial results suggest that performing a surgical intervention following a VCF *substantially increases* life expectancy overall and that performed a BKP rather than a VP *has a measurable and significant improvement on life expectancy.* These finding were true *regardless of the age of the patient.* The overall Hazard Ratio comparing Operated (any procedure) to Non-operated patients was 1.82 ± 0.13. As in previous analyses, the life expectancy analysis was performed using a set of twelve common comorbidities to account for incoming health status.

10. One additional systematic review of observational studies reporting data on the safety and effectiveness kyphoplasty that should be considered by the Washington State Health Care Authority in its assessment of kyphoplasty.

Hulme et al. [38] evaluated the safety and efficacy of vertebroplasty and kyphoplasty using the data presented in published clinical studies thru June 2005 with respect to patient pain relief, restoration of mobility, restoration of vertebral body height, complication rates, and incidence of new fractures. The authors noted that cement leakage rates were higher for vertebroplasty (41%) than kyphoplasty (9%).

11. Kyphoplasty – Safety Confirmed By Clinical Evidence

11.1 Kyphoplasty Devices and Procedure – Design Minimizes the Risk of Adverse Events

The synthesis of available evidence reveals the excellent safety profile of kyphoplasty in the treatment of vertebral compression fractures. This profile is a direct result of the purposeful design of the devices that comprise the kyphoplasty procedure that enable this minimally invasive technique to be conducted safely in the fragile elderly osteoporotic and/or cancer VCF patient population. Table 5 below describes how kyphoplasty is designed to minimize the potential adverse events that may accompany this procedure.

Table 5

Kyphoplasty - Potential Perioperative Adverse Events	**Kyphoplasty Adverse Event Risk Minimization**
Needle injuries resulting in local (typically neurologic) damage, often with no clinical consequence	To minimize such injury, placement of the kyphoplasty introducer cannulae is guided by antero-posterior and lateral fluoroscopic guidance
Bone cement extravasation may cause neurologic syndromes or pulmonary embolism.	1. The use of an inflatable bone tamp during kyphoplasty compacts the cancellous bone and creates a void 2. The compaction of the cancellous bone disrupts internal venous pathways, fills in fracture lines, and reduces cement leak pathways 3. The void allows the physician to deliver a predictable volume of highly viscous cement 4. Since bone cement is radiopaque, the likelihood of extravasation can be limited by the use of fluoroscopy. **NOTE:** These aspects of kyphoplasty are thought to reduce cement extravasation rates and are not available during a vertebroplasty procedure which does not employ an inflatable bone tamp.

This overview is based on an evaluation of available clinical data, including medical literature, to assess the safety of kyphoplasty for treating vertebral compression fractures. Five sources have been employed for this purpose: independent meta-analyses published in peer review

journals; device vigilance on an ongoing basis to estimate risk; network meta-analysis recently conducted of the best comparative evidence; FDA device MAUDE database descriptive review for unanticipated serious device or procedure related adverse events; and adverse events reported in sponsored randomized clinical trials. These data are summarized in sections 11.2 thru 11.5 below.

11.2 Kyphoplasty demonstrates a low rate of cement extravasations and complications in published meta-analyses.

The data from several recent meta-analyses support the safety of kyphoplasty and are summarized in the table below – for purposes of reference, those data reported for vertebroplasty in these studies are also provided.

Table 6

Cement Leaks and Complications	Kyphoplasty	Vertebroplasty
Extravertebral Cement Extravasations (Most with no clinical consequences)	7 – 9%[39,40,41,42,]	20 – 41%[40,41,42]
Serious and Symptomatic Complications	2%[40,43]	3.9%[40]
Symptomatic Cement Leakage	0% – 0.3%[39,42]	1.6% – 3%[39,42]

11.3 Kyphoplasty found to have a low rate of complications in the large body of peer-reviewed clinical evidence.

The results of the meta-analyses are in agreement with that of an internal Medtronic safety analysis in which 97 unique kyphoplasty cohort (n ≥10 pts.) studies were identified using the U.S. National Library of Medicine's MEDLINE® database as of April 5, 2010. The following data were obtained based on 6,426 subjects who underwent kyphoplasty:

- Total procedure-related severe adverse event rate = 1.18% (76 out of 6,426 patients)
- Rate of cement related symptomatic adverse events = 0.22% (14 out of 6,426 patients)
- Post-operative medical complications - not thought to be procedure related = 0.67% (43 of 6,426 cases)

11.4 Kyphoplasty found to have a low adverse event rate in multicenter prospective randomized controlled trials.

The low adverse event rate described in published meta-analyses is also consistent with results from two multicenter randomized controlled trials of kyphoplasty.

1. In the Fracture Reduction Evaluation (FREE) trial, 300 patients at 21 sites with VCFs due to osteoporosis were randomized to either kyphoplasty or nonsurgical management. In the kyphoplasty treatment group, there were 3/149 patients (2.0%) who had 4 device or procedure-related serious adverse events: a patient with a hematoma; a patient with a post-operative urinary tract infection and spondylitis; and a patient with an anterior cement migration after 1 year of index treatment.

2. In the Cancer Patient Fracture Evaluation (CAFE) Study, 134 patients at 21 sites with VCFs due to cancer were randomized to receive either kyphoplasty or nonsurgical management. In the kyphoplasty treatment group, there were 2/70 patients (2.9%) who had device or procedure-related serious adverse events: a patient with an intra-operative non-Q wave myocardial infarction with intermittent atrial fibrillation that was attributed to anesthesia and resolved; and a patient with a cement leakage to the disc had an adjacent fracture that occurred 1 day after the kyphoplasty procedure.

   Regarding fractures considered to be device related by study investigators, there was no difference in the number of patients with subsequent fractures when compared to the control

group in either the FREE or CAFE trial, suggesting that new fractures are not related to treatment with kyphoplasty.

11.5 Kyphoplasty found to have a low adverse event rate based on search of the MAUDE database.

The results stemming from a search of FDA's MAUDE database for kyphoplasty adverse events is also consistent with literature results. There were 309 (4.4 per 10,000 cases) unique events reported to the FDA; the majority of events were cardiopulmonary or neurologic in nature. No unanticipated serious device or procedure related adverse events were reported which are not already mentioned in the instructions for use. Given that approximately 700,000 fractures have been treated with kyphoplasty to date, this rate is also low.

In all cases, the published medical literature and data submitted to FDA's MAUDE database support the safe use of kyphoplasty and PMMA-based bone cements for the indications for use. The review of the combined data supports an acceptable safety profile for kyphoplasty. See Appendix 2

12. Kyphoplasty Is Widely Recognized By Professional Medical Societies

12.1 In view of the strong and consistently positive clinical evidence of its safety and effectiveness, kyphoplasty has been recognized for its role in the treatment of VCFs by major medical societies including:

- American Academy of Orthopedic Surgeons[44]
- American Association of Neurological Surgeons[45]
- American Medical Directors Association[46]
- American Society of Anesthesia[47]
- American Society of Interventional Pain Physicians[48]
- American Society of Interventional and Therapeutic Neuroradiology[45]
- American Society of Regional Anesthesia and Pain Medicine[47]
- American Society of Spine Radiology[45]
- North American Spine Society[49]
- Congress of Neurological Surgeons[45]
- International Multiple Myeloma Foundation[50]
- International Osteoporosis Foundation[51]
- Society of Interventional Radiology[45]

12.2 On September 3, 2010, The Society of Interventional Radiology (SIR) and the American College of Radiology, in a letter endorsed by the Washington State Radiological Society to Noridian LLC, a Medicare contractor, stated their societies' position that the clinical evidence supporting kyphoplasty (and vertebroplasty) was strong and made the following points regarding their medical necessity:[52]

> In sum, based on medical evidence, SIR considers percutaneous vertebroplasty or kyphoplasty as medically appropriate treatment when standard medical therapy has failed to relieve symptoms and any of the following criteria is met:
>
> - osteoporotic, osteolytic, osteonecrotic (i.e., Kummell disease), or steroid-induced vertebral compression fracture(s) with persistent, debilitating pain unresponsive to conservative medical management. Clinical questions to consider with regard to timing intervention include the patient's ability to accomplish activities of daily living (ADLs), excessive pain requiring high or IV narcotic dosages, skilled care needs, occurrence of additional fracture, and the risk of further vertebral collapse
> - back pain secondary to destruction of vertebral body due to osteolytic vertebral metastasis or multiple myeloma
> - acute compression fractures so painful that hospitalization is required
> - painful and/or aggressive hemangioma or eosinophilic granuloma of the spine

12.3 In addition, on September 24, 2010, the American Academy of Orthopaedic Surgeons released its *Guidelines and Evidence Report on the Treatment of Symptomatic Osteoporotic Spinal Compression Fracture"*. These Guidelines can be downloaded from the AAOS website at: http://www.aaos.org/Research/guidelines/SCFguideline.pdf.

The AAOS made the following recommendation in these guidelines:

> *"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."*

It should be noted that kyphoplasty is the ONLY therapy for the treatment and reduction of vertebral compression fractures recommended by the AAOS in this just released guideline.

13. Payer Technology Assessment and Policies – Additions and Corrections to HTA Section 1.4

Medtronic has noted that commonly accepted health technology assessments and influential national payer coverage policies were not addressed by the HTA and that incorrect information has been included within the HTA review. Copies of these policies and non-confidential HTAs are provided in Appendix 3 and summarized below in Table 7 and Table 8. Medtronic believes that these HTAs and national payer coverage policies should additionally be considered by the Washington State Health Care Authority in its assessment of kyphoplasty - corrections to mischaracterizations have been highlighted in red. Specifically:

13.1 The HTA review did not include the June 2009 California Technology Assessment Forum (CTAF) HTA entitled, *"Balloon Kyphoplasty as a Treatment for Vertebral Compression Fracture"*; it only considered the Vertebroplasty HTA conducted by (CTAF). After a critical review of the literature, CTAF determined that Kyphoplasty **met** criteria 1-2 and for criteria 3-5 it **too met criteria** for recent osteoporotic vertebral compression fractures, while criteria was not met for chronic osteoporotic, pathologic or traumatic vertebral compression fractures.

13.2 Consideration should also be given to an updated assessment conducted by the Ontario Health Technology Advisory Committee. While WA State's review of this HTA cited it being reviewed in 2004, a recent review of the procedures was done in July and August 2010

(attached in Appendix 3). The Ontario HTA concluded that, while evidence did not support the use of vertebroplasty in patients with VCFs, it did allow for kyphoplasty as a treatment after a period of failed conservative therapy.

13.3 Two U.S.-based HTA's were not included; the ECRI (Percutaneous Balloon Kyphoplasty for the Treatment of Vertebral Fractures- March 2006) and Hayes (Percutaneous Kyphoplasty Feb 28, 2008) reports. Both of these assessments are not publically available and must be purchased however the ECRI assessment deemed the clinical evidence for Kyphoplasty strong to moderate when evaluating the effectiveness of the therapy.

Additionally, Medtronic would like to submit that clarifications should be made to the Washington State Health Care Authority's HTA statement concerning kyphoplasty coverage by the Centers for Medicare and Medicaid services (CMS). While it is on the list of potential NCDs, **kyphoplasty is currently allowed and has positive coverage by all local Medicare Administrative Carriers (MACs) nationwide**. Indeed, all but two MACs **have published, active positive LCD's**, one has an active published article, and one has coverage via a fee schedule.

Listed below are the positive LCDs which Medtronic believes should be recognized by the HTA in its evaluation of kyphoplasty coverage:

- Cahaba- LCD # L30062 and draft LCD # 31425
- Cigna- LCD#31349
- First Coast Option- LCD # L20209
- Highmark- fee schedule
- NGS- retired LCD, Article # A45937
- NHIC- LCD # 11417
- Noridian- LCD # DL24383 and draft LCD # DL24383
- Palmetto- LCD # 27595
- Trailblazer- LCD # L27595
- WPS- LCD # L16088, L16089, L16090, L16091

When considering commercial payer coverage, it is common place to consider the larger most influential payers (Aetna, Wellpoint, United Healthcare and Cigna) – see highlights in Table 8 and the contents of the policies in Appendix 3.

- The WA State review only took into consideration Aetna and Cigna and to truly understand the coverage environment for kyphoplasty one should consider the other payers as well.
- For example, Wellpoint is the largest BCBS system in the United States. It has a current positive (dated 2010-Percutaneous Spinal Procedures: Vertebroplasty, Kyphoplasty and Sacroplasty) coverage policy for the therapies in question.
- United Health Care who has been a leader in strong clinical data analysis also has a positive coverage policy (Percutaneous Vertebroplasty and Kyphoplasty #20007T0300D).
- Lastly and of particular importance, Table 8 describes a Regence (BCBS WA) coverage policy that has been included in the HTA but does not even apply to these therapies. The appropriate policy which should be reviewed and given consideration is their Percutaneous Vertebroplasty and Kyphoplasty policy (2010 draft and 2009 Surgery Policy # 107).

Appendix 3 contains the majority of these coverage policies and non-confidential HTA's. While each of them varies slightly in its selection and treatment criteria, each has recognized the need to have kyphoplasty made an available treatment to patients to treat their VCFs. This has been done by allowing a fair and complete review of the current evidence and allowing coverage.

Table 7						
Previous Systematic Reviews/Technology Assessments						
Assessment (year)	Lit Search Dates	Procedure Evaluated	Evidence Base Available	Critical Appraisal	Comments	Primary Conclusions
The California Technology Assessment Forum (CTAF) Balloon Kyphoplasty as a Treatment for Vertebral Compression Fractures; 6/17/2009	Through 4/2009	Kyphoplasty	See Appendix 3	Yes	Kyphoplasty **DOES meet** criteria 1-2. Kyphoplasty **DOES meet** criterion 3-5 for recent osteoporotic vertebral compression fractures. Criterion 3-5 is **not met** for chronic osteoporotic, pathologic or traumatic vertebral compression fractures.	See Appendix 3
Ontario Health Assessment *Balloon Kyphoplasty* ***UPDATED: July & August 2010- see OTAC website***					• Vertebroplasty not supported in use of patients with VCFs. • Kyphoplasty- the OTAC recommended conservative treatment which allows the fracture to heal naturally; initiation of management of the underlying condition; patient monitoring including bone mineral density testing; and, patient education about the course of natural healing and **alternative treatment options such as kyphoplasty *if*** there is no response to conservative treatment within an appropriate time."	
ERCI *Percutaneous Balloon Kyphoplasty for the treatment of Vertebral Fractures* *March 2006*		Document is not to be duplicated-confidential			Technology is effective with strong to moderate rated evidence	
Hayes *Percutaneous Kyphoplasty* *Feb 28, 2008*		Document is not to be duplicated-confidential				

Table 8 - CMS				
Payer Technology Assessments and Policies				
Payer (year)	**Lit Search Dates**	**Evidence Base Available**	**Policy**	**Rationale/ Comments**
Centers for Medicare and Medicaid Services (CMS)	N/A See PDF file of composition of LCD policies in Appendix 3	N/A See PDF file of composition of LCD policies in Appendix 3	No NCDs or LCDs. However, vertebroplasty and kyphoplasty are potential NCD topics. **(INCORRECT STATEMENT- SEE CORRECT DATA BELOW)** • **National CMS**- vertebroplasty and kyphoplasty are potential NCD topics • **First Coast Option LCD #L20209** (coverage allowed) • **Cahaba LCD#L30062 & Draft LCD #31425** (coverage allowed) • **Highmark- fee schedule only** (coverage allowed) • **NGS- Article #A45937** (coverage allowed) • **NHIC LCD #11417** (coverage allowed) • **Noridian LCD #DL24383 & Draft LCD #DL24383** (current- coverage allowed, draft open) • **Palmetto LCD #27595** (coverage allowed) • **Trailblazer LCD #L26701** (coverage allowed) • **WPS LCD #L16088, L16089, L16090, L16091** (coverage allowed)	N/A See PDF file of composition of LCD policies in Appendix 3

Table 8 - Regence				
Payer Technology Assessments and Policies				
Payer (year)	**Lit Search Dates**	**Evidence Base Available**	**Policy**	**Rationale/ Comments**
Regence (2009) *Computer assisted navigation for orthopedic procedures of the pelvis and appendicular skeleton.* Percutaneous Vertebroplasty and Kyphoplasty (2010 Draft) & (2009 Policy) Surgery #107	Through 2009 Through 2010; See Appendix 3	2007 BCBS Tec Assessment • 1 prospective multicenter study • 1 meta-analysis See Appendix 3	• Computer assisted navigation for orthopedic procedures involving the pelvis and appendicular skeleton is considered investigational • Percutaneous vertebroplasty or kyphoplasty may be considered **medically necessary** for the treatment of the following: A. Symptomatic osteoporotic (compression) vertebral fractures of the thoracic or lumbar spine that have failed to respond to conservative treatment (e.g., analgesics, physical therapy and rest) for at least 6 weeks, or B. Severe pain due to osteolytic lesions of the spine related to multiple myeloma, or primary or metastatic spinal malignancies II. Percutaneous vertebroplasty or kyphoplasty is considered **investigational** for all other indications, including but not limited to the following: A. Vertebral hemangioma B. Acute vertebral fractures due to osteoporosis or trauma C. Stabilization of insufficiency fractures or lesions of the sacrum (sacroplasty) or coccyx (coccygeoplasty)	Recent RCTs with short to mid-term follow-up have not shown improved health outcomes with CAN. See Appendix 3

Table 8 – Anthem Wellpoint				
Payer Technology Assessments and Policies				
Payer (year)	**Lit Search Dates**	**Evidence Base Available**	**Policy**	**Rationale/ Comments**
Anthem Wellpoint (2010) *Percutaneous Spinal Procedures (Vertebroplasty, Kyphoplasty and Sacroplasty)* SURG.00067	See Appendix 3	See Appendix 3	Percutaneous vertebroplasty or kyphoplasty of the cervical, lumbar or thoracic region is considered **medically necessary** after failure of standard medical therapy when **any** of the following criteria are met: 1. Osteolytic vertebral metastasis or myeloma with severe back pain related to destruction of the vertebral body **not** involving the major part of the cortical bone, and chemotherapy and radiation therapy have failed to relieve symptoms; **OR** 2. Vertebral hemangiomas with aggressive clinical signs (severe pain or nerve compression) or aggressive radiological signs, and radiation therapy has failed to relieve symptoms; **OR** 3. Osteoporotic vertebral collapse with persistent debilitating pain which has not responded to accepted standard medical therapy as documented in the medical records. Standard medical therapy may include initial bed rest with progressive activity, analgesics, physical therapy, bracing and exercises to correct postural deformity and increase muscle tone, salmon calcitonin, bisphosphonates and calcium supplementation; OR 4. Painful vertebral eosinophilic granuloma with spinal instability; OR 5. Traumatic or steroid-induced vertebral fracture with persistent debilitating pain, which has not responded to standard medical therapy. Percutaneous sacroplasty is considered investigational and not medically necessary for all indications	See Appendix 3

Bibliography

1. Rao RD, Singrakhia MD. Painful osteoporotic vertebral fracture. Pathogenesis, evaluation, and roles of vertebroplasty and kyphoplasty in its management. J Bone Joint Surg Am. 2003 Oct;85-A(10):2010-22.
2. Antonacci MD, Mody DR, Rutz K, et al. A histologic study of fractured human vertebral bodies J Spinal Disord Tech. 2002 Apr;15(2):118-26.
3. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res. 1993 Sep;8(9):1137-48.
4. Gold DT, The clinical impact of vertebral compression fractures. Quality of life in women with osteoporosis. Bone 1996; 18(3 Suppl):185S-189S.
5. Silverman SI. The clinical consequences of vertebral compression fractures. Bone. 1992;13(suppl. 2)27-31.
6. Leech JA, Dulberg C, Kellie S, Pattee L, et al. Relationship of lung function to severity of osteoporosis in women. Am Rev Respir Dis. 1990 Jan;141(1):68-71
7. Van Schoor NM, Smit JH, Twisk JWR, et al. Impact of vertebral deformities, osteoarthritis, and other chronic diseases on quality of life: a population-based study. Osteopor Internat (2005)16: 749-756.
8. Cauley JA, Thompson DE, Ensrud KC, et al. Risk of mortality following clinical fractures. Osteoporos Int. 2000;11(7):556-61.
9. Kado D, Huang MH, Karlamangala AS, Barrett-Connor E, Greendale G. Hyperkyphotic posture predicts mortality in older community-dwelling men and women: a prospective study. J Am Ger Soc 52, 1662-7, 2004.
10. Lindsay R, Pack S, Li Z. Longitudinal progression of fracture prevalence through a population of postmenopausal women with osteoporosis. Osteoporos Int. 2005 Mar;16(3):306-12.
11. Lieberman I, Talmadge K (2005) Surgical Innovations: Kyphoplasty for women with compression fractures. Clin Rev Bone Min Metab 3:149-156).
12. Yuan HA, Brown CW, Phillips FM. Osteoporotic spinal deformity: a biomechanical rationale for the clinical consequences and treatment of vertebral body compression fractures. J Spinal Disord Tech. 2004 Jun;17(3):236-42.
13. Silverman SI. The clinical consequences of vertebral compression fractures. Bone. 1992;13(suppl. 2)27-31.
14. Oleksik Am, Ewing S, Shen WQ, van Schoor NM, Lips P. Impact of incident vertebral fractures on health-related quality of life in post-menopausal women with prevalent fractures. Osteoporosis Int. 15:861-870, 2005.
15. Phillips FM, Todd Wetzel F, Lieberman I, Campbell-Hupp M. An in vivo comparison of the potential for extravertebral cement leak after vertebroplasty and kyphoplasty. Spine 2002;27(19):2173-8; discussion 8-9.
16. Phillips FM, Wetzel TF, Lieberman I, et al. An in-vivo comparison of the potential for extravertebral cement leak after vertebroplasty and kyphoplasty. Spine 2002;27:2173-2178.
17. Radvany M. Research Reporting Standards for Percutaneous Vertebral Augmentation. J Vasc Interv Radiol 2009; 20:1279-1286)
18. Lee MJ, Dumonski M, Cahill P, et al. Percutaneous treatment of vertebral compression fractures. A meta-analysis of complications. Spine 2009;34(11):1228-1232.
19. Taylor RS, Taylor RJ, Fritzell P. Balloon kyphoplasty and vertebroplasty for vertebral compression fractures: a comparative systematic review of efficacy and safety. Spine 2006; 31:2747-55. One or more authors were paid Medtronic consultants. Medtronic supported this study.
20. Hulme PA, Krebs J, Ferguson SJ, Berlemann U. Vertebroplasty and kyphoplasty: a systematic review of 69 clinical studies. Spine 2006; 31:1983-2001. One or more authors were paid Medtronic faculty. Medtronic did not support this study.
21. Garfin SR, Yuan HA, Reiley MA. New technologies in spine: kyphoplasty and vertebroplasty for the treatment of painful osteoporotic compression fractures.Spine. 2001 Jul 15;26(14):1511-5.

22. Brunton S, Carmichael B, Gold D, et al. Vertebral compression fractures in primary care: recommendations from a consensus panel. Fam Pract. 2005 Sep;54(9):781-8.

23. Hussein MA, Vrionis FD, Allison R, Berenson J,, et al. The role of vertebral augmentation in multiple myeloma: International Myeloma Working Group Consensus Statement. Leukemia. 2008 Aug;22(8):1479-84.

24. Chung HJ, Chung KJ, Yoon HS, et al. Comparative study of balloon kyphoplasty with unilateral versus bilateral approach in osteoporotic vertebral compression fractures. Int Orthop. 2008 Dec;32(6):817-20.

25. Wardlaw D, Cummings SR, Van Meirhaeghe, J et al. Efficacy and safety of balloon kyphoplasty compared with nonsurgical care for vertebral compression fracture (FREE): a randomized controlled trial. Lancet 2009;373:1016-24.

26. CMS MEDPAR data files from CY09

27. Berenson [P2873] Blood (American Society for Hematology Annual Meeting Abstracts) 2009;114(22):2873.

28. Kumar K, Nguyen R, Bishop S. A comparative analysis of the results of vertebroplasty and kyphoplasty in osteoporotic vertebral compression fractures. Neurosurgery. 2010 Sep;67(3 Suppl Operative):171-88.

29. Komp M., Ruetten S., Godolias G. Minimally invasive therapy for functionally unstable osteoporotic vertebral fracture by means of kyphoplasty: prospective comparative study of 19 surgically and 17 conservatively treated patients. J Miner Stoffwechs 2004: 11 (Suppl 1):13-15.

30. Dong R, Chen L, Gu Y, Han G, Yang H, Tang T, Xioaqing C. Improvement in respiratory function after vertebroplasty and kyphoplasty. International Orthopedics 2009, 3:1689-94.

31. Healthcare Cost and Utilization Project website: http://www.hcup-us.ahrq.gov/nisoverview.jsp#used

32. Lad SP, Patil CG, Lad EM, et al. National trends in vertebral augmentation procedures for the treatment of vertebral compression fractures. Surg Neurol. 2009 May;71(5):580-4.

33. Zampini JM, White AP, McGuire KJ. Comparison of 5766 vertebral compression fractures treated with or without kyphoplasty. Clin Orthop Relat Res. 2010 Jul;468(7):1773-80.

34. Lau E, Ong K, Kurtz S, et al. Mortality following the diagnosis of a vertebral compression fracture in the Medicare population. J Bone Joint Surg Am. 2008 Jul;90(7):1479-86.

35. Edidin A.A., Ong K.L., Lau E., et al. Mortality Risk for Operated and Non-Operated Vertebral Fracture Patients in the U.S. Medicare Population. Osteoporos Int (2010)21:Suppl 1 S19 [abstract].

36. Kado DM, Lui LY, Ensrud KE, et al. Hyperkyphosis predicts mortality independent of vertebral osteoporosis in older women. Ann Intern Med. 2009 May 19;150(10):681-7.

37. Data on File, Medtronic Inc.

38. Hulme PA, Krebs J, Ferguson SJ, Berlemann U. Vertebroplasty and kyphoplasty: a systematic review of 69 clinical studies. Spine 2006 Aug 1;31(17):1983-2001.

39. Taylor RS, Fritzell P, Taylor RJ. Balloon kyphoplasty in the management of vertebral compression fractures: an updated systematic review and meta-analysis. Eur Spine J 2007;16:1085-100.

40. Hulme PA, Krebs J, Ferguson SJ, Berlemann U. Vertebroplasty and kyphoplasty: a systematic review of 69 clinical studies. Spine 2006;31:1983-2001.

41. Hadjipavlou AG, Tzermiadianos MN, Katonis PG, Szpalski M. Percutaneous vertebroplasty and balloon kyphoplasty for the treatment of osteoporotic vertebral compression fractures and osteolytic tumours. J Bone Joint Surg Br 2005;87:1595-604.

42. Eck JC, Nachtigall D, Humphreys SC, Hodges SD. Comparison of vertebroplasty and balloon kyphoplasty for treatment of vertebral compression fractures: a meta-analysis of the literature. Spine J 2008;8:488-97.

43. Bouza C, Lopez T, Magro A, Navalpotro L, Amate JM. Efficacy and safety of balloon kyphoplasty in the treatment of vertebral compression fractures: a systematic review. Eur Spine J 2006:1-18.

44. American Academy of Orthopaedic Surgeons Guidelines: http://www.aaos.org/Research/guidelines/SCFguideline.pdf

45. Jensen ME, McGraw JK, Cardella JF, et al. Position statement on percutaneous vertebral augmentation: a consensus statement developed by the 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. Vasc Interv Radiol. 2009 Jul;20(7 Suppl):S326-31.

46. American Medical Directors Association Guideline Update concerning kyphoplasty: http://www.cpgnews.org/O/updates.cfm

47. Practice Guidelines for Chronic Pain Management. American Society of Anesthesia. Anesthesiology 2010;112:810-33.

48. Boswell MV, Trescot AM, Datta S, et al. Interventional techniques: evidence-based practice guidelines in the management of chronic spinal pain. Pain Physician. 2007 Jan;10(1):7-111.

49. North American Spine Society Letter to CMS 2008: http://www.cms.gov/mcd/ncpc_publiccomment_popup.asp?comment_id=780

50. Hussein MA, Vrionis FD, Allison R, Berenson J, et al. The role of vertebral augmentation in multiple myeloma: International Myeloma Working Group Consensus Statement. Leukemia. 2008 Aug;22(8):1479-84.

51. International Osteoporosis Foundation. The Breaking Spine. http://www.iofbonehealth.org/publications/the-breaking-spine.html

52. Society of Interventional Radiology and the American College of Radiology to Noridian LLC: http://www.sirweb.org/misc/Noridian/SIR_Comment_Letter_Noridian.pdf