

February 19, 2019

Virginia Muir
Medical Policy Consultant
National Government Services, Inc

Dear. Ms. Muir:

In response to your email on Friday, February 15, 2019 to the CAC representatives and Subject Matter Experts regarding the Medicare Administrative Contractors (MACs) multi-jurisdictional Contractor Advisory Committee Webex meeting on March 20, 2019, 1-4 pm EST, I would like to submit this letter. It is in response to your request to provide literature regarding the strength of published evidence on Percutaneous Vertebral Augmentation (PVA) for osteoporotic Vertebral Compression Fracture (VCF).

What are specifically referenced are two methodologically controversial, randomized controlled trials that found no benefit of percutaneous vertebroplasty over sham published in 2009 and a perceived "lack of consensus on the appropriate management of osteoporotic VCFs". The 2009 sham trials have been a target of significant criticism since their publication and rightfully so. These trials published by Kallmes et al (1) and Buchbinder et al (2) found no beneficial effect of cement augmentation when vertebroplasty (VP) was compared with paraspinal injection of local anesthetic but this technique has been shown with high quality evidence to provide significant reduction of pain in a number of individuals with vertebral fractures (3, 4). The sham studies were further called into question with criticisms due to selection bias. The INVEST trial (Kallmes et al) had to screen 1812 patients to get only 131 enrolled in the study and the trial from Buchbinder et al took 4.5 years to only enrol 78 patients. The Buchbinder trial had an unacceptably high percentage (67%) of cases performed by one physician with the primary variable being the difference in mean pain not a difference in the clinically relevant response rate which, for a one point difference, would've required 120 patients in each group not the 35 and 38 patients that were enrolled. The INVEST trial had an unacceptably high cross over rate with 51% of sham patients crossing over to vertebroplasty with only 13% of vertebroplasty patients crossing over. The crossover and non-crossover patients were also significantly different after treatment. The Invest trial also had an unacceptably low initial pain score of a three out of ten to be included in the trial. This trial also had difficulties blinding patients with 63% of the patients correctly guessing their treatment. The Invest trial also allowed workers compensation patients who are nearly always prohibited from studies like this due to the potential for secondary gain. Both studies had no description of a clinical exam to determine if pain resulted from the vertebral compression fracture or another problem and the Buchbinder study only had an assessment of "overall pain" rather than an assessment related to axial back pain as is seen with spine fractures. Both studies suffered from non-uniform diagnostic criteria for vertebral compression fractures (VCF's) and most fractures were greater than three months old when pain from many VCF's starts to decrease. In the Buchbinder trial the mean amount of bone cement injected was 2.8cc which is only a sufficient amount to treat females at the T6 level or higher (5 - 13) and an amount that led other experts to conclude that this "strongly indicates that the treatment arm includes patients who were not treated in a reasonably effective manner" (14).

What is unfathomable is for any recommendations to be made based on the precarious statistical support for the outcome with the underpowered Invest trial only attaining a p value of 0.06 just a tiny statistical fraction away from the conclusion that vertebroplasty was significantly superior to sham. In fact if the same response was kept but the number of study patients would have been the original goal of 250 patients the p value would have been equal to 0.01 favoring vertebroplasty over sham. Additionally if a single patient in the vertebroplasty group would have had a more favorable response or vice versa in the sham group the conclusion of the trial would have been exactly opposite. The statistical margin for making the conclusion of non-superiority of vertebroplasty in the Invest trial was as thin as it possibly could have been to still come to its highly controversial conclusion.

One of the primary reasons that the 2009 studies remain controversial is the active treatment arms of the trials were far less effective for pain relief than nearly all other trials in vertebral augmentation. The

pain reduction in the Kallmes and Buchbinder trials was 3.0 and 2.3 point on the Numeric Rating Scale (NRS). This is starkly different from other well-recognized randomized control trials (RCTs) including the Vertos 2 trial with a 5.7 point reduction and the KAST trial with a 7.0-point reduction (15, 16). Even the post-market EVOLVE trial demonstrated a dramatic pain reduction of 6.3 points and the patient reported outcomes (PRO's) of the largest vertebral augmentation registry worldwide was a much higher 6.7 point reduction (17, 18). So if the 2009 sham trials conclude there is no difference in pain relief compared to sham, this comparison is made with results that are, at best, less than half as good as is seen in many communities through the United States on a daily basis. The logical conclusion of this is that the treatment arms in the sham trials were not conducted optimally as compared to nearly all other good quality data available for comparison.

Given the above findings of the 2009 sham trials it is not surprising that these articles were subsequently discredited due to fundamental flaws and downgraded to Level II evidence-based on the inclusion and exclusion criteria in both of the trials and the crossover rate in the Kallmes trial (19). These articles were replete with flaws both in design and execution of the trials.

Since 2009, there have been 6 prospective RCTs on vertebral augmentation (VA) for the treatment of osteoporotic vertebral compression fractures (OVCFs) and 5 of them have shown superior results with vertebral augmentation (VA) as compared with non-surgical management (NSM) (20 – 27). A meta-analysis published in 2012 (28) and one published in 2013 (19) conclude that osseous augmentation is a preferred treatment option for patients who have painful OVCFs. The most exhaustive meta-analysis published to date analysed all Level I and Level II data and showed that VA was superior to NSM in the treatment of osteoporotic OVCFs in regard to reducing pain and subsequent fractures (28).

Despite all of the positive meta-analysis articles there are two articles published recently, including a review (29) and a meta-analysis (30) which represent inconsistent data or biased data reporting with an overemphasis on certain trial types and a complete exclusion of other types of data with reporting conclusions that are partially representative or not representative of the data. Unsurprisingly there were many authors in common with the negative literature published to date in these biased analyses. This along with examples of this biased data reporting have been compared by Beall, et. al. to the current body of published literature germane to this topic (31).

As was referred to in the recent email from Virginia Muir there has been “several recent publications” that “further question the value of PVA”. Among these include Vertos 4 and the Second ASBMR Task Force Report, appearing in *Journal of Bone and Mineral Research* (32, 33). The Task Force's recommendation as published in the *Journal of Bone and Mineral Research* (JBMR) is dangerous and can put patients at an increased risk of morbidity and death. The JBMR manuscript calls the members of the Task Force experts but it is difficult for me to see how they are experts in vertebral augmentation. Most of the authors of the ASBMR Task Force do not even perform the procedure they are writing about and the ones that do perform vertebral augmentation still do it after writing negative articles about it (1, 2, 32, 33). These Task Force members are some of the same individuals who authored the 2009 sham trials with three of the authors of the Task Force articles also appearing as authors of the sham trials. There are many other authors of the Task Force that have written consistently negative articles about vertebral augmentation and other spine procedures in general (33). In general it is ill-advised to continue to perform a procedure that has been found to be ineffective but it has been documented that authors of these trials continue to do so (31). Authors that continue to perform a procedure after authoring a manuscript that does not support the performance of the procedure means that either they do not believe their study's conclusions or that they continue to do it for other reasons that are unclear to me. It is also atypical to write a manuscript, especially a highly critical and controversial one, about a procedure that most of the authors do not do personally but the ASBMR Task Force is filled with authors from the departments of Internal Medicine, Clinical Sciences, Epidemiology, Human Metabolism, etc. that have never performed any interventional spine procedures in their current professional positions.

The dangerous part of the Task Force's recommendations is that the authors say there is insufficient evidence to recommend vertebroplasty or kyphoplasty. This will inevitably decrease the number of patients treated, a phenomenon that has unfortunately been seen previously right after two of the five articles they discussed were published in 2009. What happened after the publications is known, documented and very unfortunate as the number of patients being treated plunged and an estimated 75,452 patient were at higher mortality risk and an estimated 6,814 lives were lost due to a change in treatment patterns with less patients

receiving vertebral augmentation (34). This situation seems to have not even been addressed by the task force. It's not that it is an esoteric fact that vertebral augmentation is demonstrably lifesaving and life prolonging. This has been studied extensively by many different authors and in many different countries including Germany, Taiwan, Sweden, South Korea, Finland and there are many studies in the United States that document vertebral augmentation decreases morbidity, decreases mortality and prolongs life (35-43).

The task force points out that there is a lack of consensus regarding the efficacy of vertebral augmentation but completely ignores a salient publication from a multidisciplinary group of experts addressing that exact issue (44). These consensus recommendations were done by a multispecialty group of physicians including experts who perform the procedures and used the RAND/UCLA Appropriateness Method to produce a clinical care pathway. So there actually is consensus that has been formally developed into a complete clinical care pathway and to quote from the paper itself "nearly all variables showed high statistical significance and their impact on vertebral augmentation was cumulative: the higher number of unfavorable factors the greater the weight of the decision to perform vertebral augmentation rather than non-surgical management". The recommendations give firm recommendations that are extremely favorable to vertebral augmentation and provides guidelines on how patients should be appropriately treated using real data and an established process (44). This was completely ignored by the participants on the ASBMR Task Force.

The Task Force also states that there is "insufficient evidence to support kyphoplasty over non-surgical management (NSM), percutaneous vertebroplasty, vertebral body stenting or Kiva" but don't acknowledge that a large kyphoplasty RCT, the FREE Trial published in 2009, provided Level 1 evidence supporting kyphoplasty over NSM as a significantly better treatment (20). A recent meta-analysis by Papanastassiou showed kyphoplasty provided significantly better quality of life improvements and better pain relief than vertebroplasty (28). The meta-analysis examined 1,587 articles in the English language including 27 Level I or II articles compared to the task force's five articles.

One has to wonder why the Task Force examined only five articles. It should also be noted that the Task Force only examined the vertebroplasty versus sham trials. Despite this severely limited dataset, this did not stop the Task Force from making recommendations about kyphoplasty which is a different procedure than vertebroplasty that has been shown to provide better outcomes (28). The Task Force also did not discuss the fact that the three negative articles showing no difference in vertebroplasty and sham used a different sham than the two articles that showed vertebroplasty was significantly better than sham. They stated that "a sham procedure means that local anesthetic was administered to the skin and the procedure was simulated" which is only true for the two positive trials not the three negative ones. The negative articles used a sham that injected anesthetic onto the bone in the location of the medial branch of the dorsal ramus, a technique that has Level I evidence supporting its efficacy in significantly decreasing back pain (45, 46). So not only is this not a sham, it is an active treatment that has been shown to significantly decrease back pain. This is easily seen if you look at the "sham" from the recently published Vertos 4 trial which decreased the pain by a whopping 4.75 points on the numerical rating scale (NRS) (32). So how does this rate in regard to pain relief? Better than spine injections, radiofrequency ablations, neuromodulation, targeted drug delivery, total hip arthroplasty and virtually everything we do in medicine (47-53). Yes, that's correct, even one of the gold standards in orthopedic surgery, the hip replacement, is not significantly better when compared to the sham of Vertos 4. It seems that with this magnitude of a response the experts in the Task Force would have recognized that the sham was not a sham but an active treatment and that the amount of pain relief gained was so large that it is a benchmark that almost nothing will significantly outperform it. This is treatment nihilism and something that if applied will cause patients to suffer higher rates of morbidity and mortality. We can illustrate this by calculating the Number Needed to Treat (NNT) which is the number of patients you need to treat to prevent one bad outcome. To put this into perspective the NNT for patients taking aspirin for 1 year to prevent symptoms of a heart attack for 1 person is 1667, compared to 1 in 3000 for stroke (54). The NNT for vertebral augmentation to save one life at one year is 15. This means that, statistically, only 15 patients need to be treated with vertebral augmentation to save one life if the outcomes are followed up to one year (55). Compare this to coronary artery disease, where studies of coronary angioplasty and stent placement have shown there is no number of patients that one can treat in five years of follow-up to achieve any benefit (56). The task force's recommendations are therefore not only based on very questionable literature selection but if adopted will almost certainly result in harm to patients suffering from vertebral compression fractures.

The Task Force are recommending not performing a procedure based on five articles and almost ignore the two sham trials that were positive and completely discount the large body of literature on vertebral augmentation which has more articles than any other procedure in spine. There are about 250 articles on the subject published per year including very high quality RCT's and other large datasets that clearly demonstrate how well vertebral augmentation works in the typical patients it is intended for. It has been mentioned that the benchmark for the sham surgery in Vertos 4 is an almost insurmountable standard for pain relief and that virtually nothing in medicine outpaces this. A logical question then is what does better than the 4.75 point reduction in pain combined with a minimal clinically important difference of 1.5 points to total a level of pain reduction of 6.25 points to attain statistical significance? The answer is Kyphoplasty. In the largest clinical trial ever done on kyphoplasty and one that used Medicare rules for treatment the pain reduction in this group of 354 patients averaged a 6.3 (17). The world's largest registry recently completed in the United States showed real world results on data collected from sites around the country and featured a mean pain score reduction of 6.7 points and a median pain reduction of 9.0 points (18). In addition to being highly effective it was highly safe with only one adverse event in the registry and no persistently symptomatic significant adverse events in the largest kyphoplasty trial. The authors of the task force reached another incorrect conclusion when they stated "there is limited evidence to determine the risk of serious adverse events related to percutaneous vertebroplasty or kyphoplasty". It is obvious that they either didn't examine these large datasets or perhaps don't even know of their existence.

The Task Force calls for more placebo trials. The request for more data is routine when appropriate but robust, high-level literature already exists on this subject and the authors should be well aware of that fact. The Task Force recommends the treatment of the underlying osteoporosis that gives rise to osteoporotic vertebral compression fractures. Ironically, the medications to treat osteoporosis are primarily developed by using active comparators rather than sham trials because of a mortality benefit of 11% as reported by Bolland et al when comparing anti-resorptive osteoporotic medications to placebo (57). When this was found a debate ensued about using placebo-controlled studies because they can't be ethically justified by regulatory preferences, local Institutional Review Board approvals or by informed consent from the participants (58). The lack of ethical appropriateness was emphasized by many citing the fifth revision of the Declaration of Helsinki (October 2000) World Medical Association (WMA) which reinforces the longstanding prohibition against offering placebo instead of effective therapy. The WMA left no doubt that if a beneficial treatment for a condition has already been recognised, it is unethical to offer placebo in place of such treatment to anyone in a study of the same condition. Because of this, placebo controlled trials for osteoporotic medications are, for the most part, not conducted in the United States anymore. The mortality reduction for antiresorptive osteoporosis medications is 11% compared to 24% for vertebroplasty and 55% for kyphoplasty but that does not seem to have had any effect on the ASBMR Task Force's call for more placebo controlled studies (33).

Summary

It is our opinion that the authors of the ASBMR Task Force did not have the appropriate composition of individuals to be able to provide expert recommendations and reached the incorrect conclusions throughout their review. The Task Force was comprised of people who do not perform the procedure and individuals who do not believe their own recommendations and continue to perform the procedure. The Task Force completely ignores the fact that vertebral augmentation is one of the very few things in medicine that is demonstrably lifesaving and life prolonging and can statistically save a life for every 15 patients treated. It is our opinion that previous manuscripts published by members of the Task Force have produced the result of fewer patients treated and a consequent increase in the morbidity and mortality suffered by this patient population. The Task Force incorrectly states that there is a lack of consensus for treatment when there are published consensus recommendations by a multispecialty group of experts. The Task Force only examined five papers out of the thousands that have been produced and base their recommendation on only three of the five without appearing to understand what type of sham was used in the sham trials. The Task Force clearly does not appreciate the fact that the sham outcome in the most recent of the three negative trials is an active treatment, not a sham. This creates a benchmark for pain relief comparison that almost nothing in medicine can exceed it except for, ironically, kyphoplasty. These impressive results from kyphoplasty should be well known given that they were produced by the largest kyphoplasty trial ever done

and the world largest vertebral augmentation registry but surprisingly these works were not even acknowledged by the Task Force. They even called for more placebo controlled studies when placebo controlled studies are widely recognized to be unethical to offer in place of a treatment known to be beneficial in a study of the same condition. It is our final conclusion that the Task Force's recommendations are not properly grounded in the extensive literature on the topic and the reality of today's treatment of vertebral compression fractures. It is our data supported expert opinion that, if adopted, these recommendations will result in increased morbidity, suffering and death in our patients.

Comments submitted for as a SME (Subject Matter Expert) for input at the multi-jurisdictional Contractor Advisory Committee (CAC) via Webex on March 20, 2019, 1-4 pm EST by:

Douglas P Beall, M.D.

Society of Interventional Radiology Representative to the Multi-Specialty Pain Work Group

405-213-9639

db@clinrad.org

Letter Supported by:

Societies

1. Society of Interventional Radiology
2. North American Spine Society
3. American Society of Spine Radiology
4. North American Neuromodulation Society
5. American Society of Neuroradiology
6. International Society for the Advancement of Spine Surgery
7. Oregon Society of Interventional Pain Physicians
8. Outpatient Endovascular and Interventional Society

Groups

1. VIR Chicago
2. National Spine and Pain Centers
3. Lakeland Vascular Institute
4. Clinical Radiology of Oklahoma

Individuals

1. Peter L. Munk, M.D.
2. Luke E Sewall, M.D.
3. Devin Datta, M.D.
4. Don A Bell, M.D.
5. Daniel Kendall, D.O.
6. Peter Staats, M.D.
7. Sean Tutton, M.D.
8. Kiran Tamirisa, M.D.
9. Athos Patsalides MD MPH
10. David J Shelley, MD
11. Gunnar Andersson, M.D.
12. Nilesh M Patel MD
13. Neal H Shonnard, M.D.
14. Jeffrey C. Howard, MD
15. Brad Goodman, M.D.
16. Joshua Tepper, MD

17. Morgan Lorio, M.D.
18. Porter McRoberts, M.D.
19. Douglas P Beall, M.D.
20. Derrick Wagoner, M.D.
21. Edward Yoon, M.D.
22. Peter Staats, M.D.
23. James R. Webb, M.D.
24. Michael Budler, M.D.
25. Larry Whitney MD
26. Fakhir Elmasri MD
27. Venkat Tummala MD
28. Jong Park MD
29. Kurt Gordon MD
30. Husam Habboub MD
31. Larone Campbell MD
32. Sigurd Berven, M.D.
33. Kieran Murphy, M.D.
34. Thomas F Gleason MD
35. Jeffrey D. Coe, MD
36. Lawrence Jay Epstein, MD
37. Keith Kortman, M.D.
38. Luke Liu, M.D.
39. Ali El-Mohandes, M.D.
40. John Allen, M.D.
41. Jeff Himmelberg, M.D.
42. John Strobel, M.D.
43. David M. Christensen, MD
44. Gregory Moore, M.D.
45. Chad Stephens, M.D.
46. Ayad Agha, M.D.
47. Jack Jennings, M.D.
48. David Enterline, M.D.
49. Jason S. Brower, M.D.
50. Bart Dolmatch, M.D.
51. Mark D. Jacobson, MD
52. Nam D Tran, MD, PhD
53. E. Jeffery Donner, M.D.
54. Bradley W. Dick, MD,
55. Michael J. DePalma, MD
56. Evert-Jan Verschuyf, M.D.
57. Olivier Clerk-Lamalice, M.D.
58. Michael Frey, M.D.
59. Richard S. Obedian, M.D.
60. Keith G H Schroeder, MD
61. Thomas F Gleason MD
62. Dawood Sayed M.D.
63. Robert W. Gordon, M.D.
64. Ashish G. Shanbhag, M.D.
65. Morgan Lorio, M.D.
66. Thomas Andreshak MD
67. Michael E Pfister, MD
68. Alexis Kelekis, M.D.
69. Jerry Niedzwiecki, M.D.
70. Steven S. Hughes MD
71. Ryon Hennessy, MD

72. Ramsey Abadir
73. John Perl II M.D.
74. Steven Garfin, M.D.
75. Isadore H. Lieberman, M.D.
76. Hansen Yuan, M.D.

References

1. Kallmes DF, Comstock BA, Heagerty PJ, Turner JA, Wilson DJ, Diamond TH, Edwards R, Gray LA, Stout L, Owen S, Hollingworth W, Ghdoke B, Annesley-Williams DJ, Ralston SH, Jarvik JG. A randomized trial of vertebroplasty for osteoporotic spinal fractures. *N Engl J Med* 2009; 361:569-579.
2. Buchbinder R, Osborne RH, Ebeling PR, Wark JD, Mitchell P, Wriedt C, Graves S, Staples MP, Murphy B. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. *N Engl J Med* 2009; 361:557-568.
3. Wilson DJ, Owen S, Corkill RA. Facet joint injections as a means of reducing the need for vertebroplasty in insufficiency fractures of the spine. *European radiology* 2011;21:1772-8.
4. Im TS, Lee JW, Lee E, Kang Y, Ahn JM, Kang HS. Effects of Facet Joint Injection Reducing the Need for Percutaneous Vertebroplasty in Vertebral Compression Fractures. *Cardiovasc Intervent Radiol* 2016;39:740-5.
5. Luo, et al. Mechanical efficacy of vertebroplasty – Influence of cement type, BMD, fracture severity and disc degeneration. *Bone* 40(2007)1110-1119.
6. Gailibert P, et al. Note preliminaire sur le traitement des angiomes vertebraux par vertebroplastie acrylique percutanee. *Neurochirurgie* 1987;33:166-168
7. Giannitsios D, et al. High Cement Viscosity Reduces Leakage Risk in Vertebroplasty. *European Cells and Materials* Vol. 10 Suppl. 3, 2005 (page 54).
8. Schlegel UJ, et. al. Efficacy of vacuum bone cement mixing systems in reducing methylmethacrylate fume exposure: comparison of 7 different mixing devices and hand mixing. *Acta orthop Scan*; 75(5):559-66.
9. Fuchs M, et. al. Exposure of the surgeon and radiation during surgery. *International Orthopedics (SICOT)* (1998) 22:153-156.
10. McGraw JK, et al.. Prospective Evaluation of Pain Relief in 100 Patients Undergoing Percutaneous Vertebroplasty: Results and Follow-up. *J Vasc Interv Radiol* 2002;13:883-886.
11. Do HM et. al.. Prospective analysis of clinical outcomes after percutaneous vertebroplasty for painful osteoporotic vertebral body fractures. *Am J Neuroradiol* 2005;26:1623-28.
12. Zoarski GH, et. al. Percutaneous Vertebroplasty for osteoporotic compression fractures: quantitative prospective evaluation of long term outcomes *J Vasc Interv Radiol* 2002;13:139-48.
13. Molloy S, et. al. Effect of Cement Volume and Placement on Mechanical-Property Restoration Resulting from Vertebroplasty. *AJNR* 26:401-404, February 2006.
14. Boszczyk B. Volume matters: a review of procedural details of two randomized controlled vertebroplasty trials of 2009. *Eur Spine J*. 2010 Nov;19(11):1837-40. doi: 10.1007/s00586-010-1525-4. Epub 2010 Aug 5.
15. Klazen CA, Lohle PN, de Vries J, Jansen FH, Tielbeek AV, Blonk MC, et al. Vertebroplasty versus conservative treatment in acute osteoporotic vertebral compression fractures (Vertos II): An open-label randomized trial. *Lancet*. 2010;376:1085–92.
16. Tutton SM, Pflugmacher R, Davidian M, Beall DP, Facchini FR, Garfin SR. KAST Study: The Kiva(R) System as a Vertebral Augmentation Treatment - A Safety and Effectiveness Trial: A Randomized, Non-inferiority Trial Comparing the Kiva(R) System to Balloon Kyphoplasty in Treatment of Osteoporotic Vertebral Compression Fractures. *Spine*: Post Acceptance: March 27, 2015. doi: 10.1097/BRS.0000000000000906.
17. Beall DP, Chambers MF, Thomas SM, Amburgy J, Webb JR, Goodman B, Datta D, Easton R, Linville D, Talati S, Tillman JR. Prospective and Multicenter Evaluation of Outcomes for Quality of Life and Activities of Daily Living for Balloon Kyphoplasty in the Treatment of Vertebral Compression Fractures: The EVOLVE Trial. *J of Neurosurgery* 0:1–11, 2018 DOI:10.1093/neuros/nyy017.
18. Beall DP, Shonnard NH, Berven SH, Anderson PA, Norwitz J, Wagoner D, Khor S, Beall DP. The US Vertebral Augmentation Registry: Findings from the World's Largest Registry of Vertebroplasty and

Kyphoplasty. *European Percutaneous Spine Intervention and Vertebroplasty Workshop*. Paris, France. February 1, 2019.

19. Anderson PA, Froysheter AB, Tontz WL. Meta- analysis of vertebral augmentation compared with conservative treatment for osteoporotic spinal fractures. *Journal of bone and mineral research*. 2013 Feb 1;28(2):372-82.
20. Boonen S, Van Meirhaeghe J, Bastian L, Cummings SR, Ranstam J, Tillman JB, Eastell R, Talmadge K, Wardlaw D. Balloon kyphoplasty for the treatment of acute vertebral compression fractures: 2-year results from a randomized trial. *J Bone Miner Res* 2011; 26:1627-1637.
21. Van Meirhaeghe J, Bastian L, Boonen S, Ranstam J, Tillman JB, Wardlaw D; FREE investigators. A randomized trial of balloon kyphoplasty and non-surgical management for treating acute vertebral compression fractures: Vertebral body kyphosis correction and surgical parameters. *Spine (Phila Pa 1976)* 2013; 38:971-893.
22. Voormolen MH, Mali WP, Lohle PN, Fransen H, Lampmann LE, van der Graaf Y, Juttman JR, Janssens X, Verhaar HJ. Percutaneous vertebroplasty compared with optimal pain medication treatment: Short-term clinical outcome of patients with subacute or chronic painful osteoporotic vertebral compression fractures. The VERTOS study. *AJNR Am J Neuroradiol* 2007; 28:555-560.
23. Farrokhi MR, Alibai E, Maghami Z. Randomized controlled trial of percutaneous vertebroplasty versus optimal medical management for the relief of pain and disability in acute osteoporotic vertebral compression fractures. *J Neurosurg Spine* 2011; 14:561-569.
24. Klazen CA, Lohle PN, de Vries J, Jansen FH, Tielbeek AV, Blonk MC, Venmans A, van Rooij WJ, Schoemaker MC, Juttman JR, Lo TH, Verhaar HJ, van der Graaf Y, van Everdingen KJ, Muller AF, Elgersma OE, Halkema DR, Fransen H, Janssens X, Buskens E, Malli WP. Vertebroplasty versus conservative treatment in acute osteoporotic vertebral compression fractures (Vertos II): An open label randomised trial. *Lancet* 2010; 376:1085-1092.
25. Rousing R, Andersen MO, Jespersen SM, Thomsen K, Lauritsen J. Percutaneous vertebroplasty compared to conservative treatment in patients with painful acute or subacute osteoporotic vertebral fractures: Three-months follow-up in a clinical randomized study. *Spine (Phila Pa 1976)* 2009; 34:1349-1354.
26. Rousing R, Hansen KL, Andersen MO, Jespersen SM, Thomsen K, Lauritsen JM. Twelve-month follow-up in forty-nine patients with acute/semiacute osteoporotic vertebral fractures treated conservatively or with percutaneous vertebroplasty: A clinical randomized study. *Spine (Phila Pa 1976)* 2010; 35:478-482.
27. Blasco J, Martinez-Ferrer A, Macho J, San Roman L, Pomés J, Carrasco J, Monegal A, Guañabens N, Peris P. Effect of vertebroplasty on pain relief, quality of life, and the incidence of new vertebral fractures: A 12-month randomized follow-up, controlled trial. *J Bone Miner Res* 2012; 27:1159-1166.
28. Papanastassiou ID, Phillips FM, Van Meirhaeghe J, Berenson JR, Andersson GB, Chung G, Small BJ, Aghayev K, Vrionis FD. Comparing effects of kyphoplasty, vertebroplasty, and nonsurgical management in a systematic review of randomized and non-randomized controlled studies. *Eur Spine J* 2012; 21:1826-1843.
29. Buchbinder R, Golmohammadi K, Johnston RV, Owen RJ, Homik J, Jones A, Dhillon SS, Kallmes DF, Lambert RG. Percutaneous vertebroplasty for osteoporotic vertebral compression fracture. *Cochrane Database Syst Rev* 2015; (4):CD006349.
30. Gu CN, Brinjikji W, Evans AJ, Murad MH, Kallmes DF. Outcomes of vertebroplasty compared with kyphoplasty: A systematic review and meta-analysis. *J Neurointerv Surg* 2016; 8:636-642.
31. Beall DP, Tutton SM, Murphy K, Olan W, Warner C, Test JB. Analysis of Reporting Bias in Vertebral Augmentation. *Pain Physician*. 2017 Nov;20(7):E1081-E1090.
32. Firanesco CE, Vries J, Lodder P, Venmans A, Schoemaker M, Smeet A, Donga E, Juttman J, Klazen C, Elgersma O, Jansen F, Tielbeek A, Boukrab I, Schonenberg K, van Rooij W, Hirsch JA, Lohle PNM. Vertebroplasty versus sham procedure for painful acute osteoporotic vertebral compression fractures (VERTOS IV): randomized sham controlled clinical trial. *BMJ* 2018;360:k1551. <http://dx.doi.org/10.1136/bmj.k1551>
33. Ebeling PR¹, Akesson K², Bauer DC³, Buchbinder R⁴, Eastell R⁵, Fink HA⁶, Giangregorio L⁷, Guanabens N⁸, Kado D⁹, Kallmes D¹⁰, Katzman W¹¹, Rodriguez A¹, Wermers R¹², Wilson

- HA¹³, Bouxsein ML¹⁴. The Efficacy and Safety of Vertebral Augmentation: A Second ASBMR Task Force Report. *J Bone Miner Res.* 2019 Jan;34(1):3-21. doi: 10.1002/jbmr.3653.
34. Ong KL, Beall DP, Frohbergh M, Lau E, Hirsch JA. Reply to "At what price decreased mortality risk?". *Osteoporos Int.* 29(8), 1929-1930. 2018 May 3., doi: 10.1007/s00198-018-4551-4.
35. Edidin A, et al. Mortality Risk for Operated and Non-Operated Vertebral Fracture Patients in the Medicare Population. *JBMR*, 2011: Feb 9. DOI: 10.1002/jbmr.353
36. Chen AT, Cohen DB, Skolasky RL. Impact of nonoperative treatment, vertebroplasty, and kyphoplasty on survival and morbidity after vertebral compression fracture in the Medicare population. *J Bone Joint Surg Am.* 2013 Oct 2;95(19):1729-36. doi: 10.2106/JBJS.K.01649.
37. 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. doi: 10.1007/s11999-010-1279-7.
38. Park J, Park S, Lee HJ, Lee C, Chang B, Kim H. Mortality following benign sacral insufficiency fracture and associated risk factors. *Arch Osteoporos* (2017) 12: 100. <https://doi.org/10.1007/s11657-017-0395-3>
39. Lange A, Kasperk C, Alvares L, Sauermann S, Braun S. Survival and Cost Comparison of Kyphoplasty and Percutaneous Vertebroplasty Using German Claims Data. *Spine* 2014;39:318–326
40. Edidin AA¹, Ong KL, Lau E, Kurtz SM. Morbidity and Mortality after Vertebral Fractures: Comparison of Vertebral Augmentation and Non-Operative Management in the Medicare Population. *Spine (Phila Pa 1976)*. 2015 May 27.
41. Kanis JA, Oden A, Johnell O, et al. Excess mortality after hospitalisation for vertebral fracture. *Osteoporos Int* 2004;15:108-112
42. Lin JH, Chien LN, Tsai WL, et al. Early vertebroplasty associated with a lower risk of mortality and respiratory failure in aged patients with painful vertebral compression fractures. *Spine J* 2017
43. Niemi-Nikkola, Ville, BM^{*†}; Saijets, Nelli, BM^{*†}; Ylipoussu, Henriikka, BM^{*†}; Kinnunen, Pietari, MD, PhD[‡]; Pesälä, Juha, MD[‡]; Mäkelä, Pirkka, MD[‡]; Alen, Markku, MD, PhD^{*§}; Kallinen, Mauri, MD, PhD^{*§}; Vainionpää, Aki, MD, PhD^{*§¶} Long-term Posttraumatic Survival of Spinal Fracture Patients in Northern Finland, *Spine: December 1, 2018 - Volume 43 - Issue 23 - p 1657-1663.* doi: 10.1097/BRS.0000000000002687.
44. Hirsch JA, Beall DP, Chambers MR, Andreshak TG, Brook AL, Bruel BM, Deen HG, Gerszten PC, Kreiner DS, Sansur CA, Tutton SM, van der Meer P, Stoevelaar HJ. Management of vertebral fragility fractures: A clinical care pathway developed by a multispecialty panel using the RAND/UCLA Appropriateness Method. *Spine J.* 2018 Aug 7. pii: S1529-9430(18)31084-2. doi:10.1016/j.spinee.2018.07.025. [Epub ahead of print] PMID: 30096377
45. Wilson DJ, Owen S, Corkill RA. Facet joint injections as a means of reducing the need for vertebroplasty in insufficiency fractures of the spine. *European radiology* 2011;21:1772-8.
46. Im TS, Lee JW, Lee E, Kang Y, Ahn JM, Kang HS. Effects of Facet Joint Injection Reducing the Need for Percutaneous Vertebroplasty in Vertebral Compression Fractures. *Cardiovasc Intervent Radiol* 2016;39:740-5.
47. Nath S, Nath CA, Pettersson K. Percutaneous lumbar zygapophysial (Facet) joint neurotomy using radiofrequency current, in the management of chronic low back pain: a randomized double-blind trial. *Spine* 2008; 33:1291-7.
48. Tekin I, Mirzai H, Ok G, Erbuyun K, Vatansever D. A comparison of conventional and pulsed radiofrequency denervation in the treatment of chronic facet joint pain. *Clin J Pain* 2007; 23:524-9.
49. Lakemeier S, Lind M, Schultz W, Fuchs-Winkelmann S, Timmesfeld N, Foelsch C, Peterlain CD. A comparison of intraarticular lumbar facet joint steroid injections and lumbar facet joint radiofrequency denervation in the treatment of low back pain: a randomized, controlled, double-blind trial. *Anesth Analg* 2013; 117:228-235.
50. Fischgrund, J. S., Rhyne, A., Franke, J., Sasso, R., Kitchel, S., Bae, H., et al. (2018). Intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: a prospective randomized double-blind sham-controlled multi-center study. *European Spine Journal*, 1–11.
51. Manchikanti L, Cash KA, McManus CD, Pampati V. Fluoroscopic caudal epidural injections in managing

chronic axial low back pain without disc herniation, radiculitis, or facet joint pain. *J Pain Res.* 2012;5:381–90. doi: 10.2147/JPR.S35924.

52. Kapural, Leonardo, Cong Yu, Matthew W. Doust, Bradford E. Gliner, Ricardo Vallejo, B. Todd Sitzman, Kasra Amirdelfan, DonnaM. Morgan, Lora L. Brown, Thomas L. Yearwood, Richard Bundschu, Allen Burton, Thomas Yang, Ramsin Benyamin, and AbramH. Burgher. "188 Randomized Controlled Clinical Trial Evaluating the Safety and Effectiveness of 10 KHz High-Frequency and Traditional Low-Frequency Stimulation for the Treatment of Chronic Back and Leg Pain." *Anesthesiology Pain Med* Newly Published on 07 2015: doi:10.1097/ALN.0000000000000774
53. Rolfson O, Dahlberg L E, Nilsson J A, Malchau H, Garellick G. Variables determining outcome in total hip replacement surgery. *J Bone Joint Surg Br* 2009; 91(2): 157–61.
54. Antithrombotic Trialists Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet.* 2009; 373(9678); 1849-60.
55. Number needed to treat with vertebral augmentation to save a life sheds light on the real world challenges of blinded trials (submitted for publication)
56. Stergiopoulos K, Boden WE, Hartigan P, et al. Percutaneous coronary intervention outcomes in patients with stable obstructive coronary artery disease and myocardial ischemia: a collaborative meta-analysis of contemporary randomized clinical trials. *JAMA Intern Med.* 2014;174(2):232–240.
57. Bolland, Mark J., Andrew B. Grey, Greg D. Gamble, and Ian R. Reid. "Effect of osteoporosis treatment on mortality: a meta-analysis." *The Journal of Clinical Endocrinology & Metabolism* 95, no. 3 (2010): 1174-1181.
58. Stein MC, Ray WA. The Ethics of Placebo in Studies with Fracture End Points in Osteoporosis. *N Engl J Med* 2010; 363:1367-1370. DOI: 10.1056/NEJMs1006120.