March 30, 2020

Noridian Healthcare Solutions, LLC
Attention: LCD Comments
PO Box 6781
Fargo, ND 58108-6781

via email: policydraft@noridian.com

Re: Percutaneous Vertebral Augmentation (PVA) for Osteoporotic Vertebral Compression Fracture (VCF) (L34228)

To Whom It May Concern:

On behalf of representatives of twelve medical specialty societies, comprising physicians who utilize and/or perform percutaneous vertebral augmentation procedures, we would like to take this opportunity to share comments regarding Noridian's Local Coverage Determination for Percutaneous Vertebral Augmentation for Osteoporotic Vertebral Compression Fracture (L34228). We have significant concerns with the proposed LCD's exclusion from treatment all fractures over six weeks old and the requirement of a multidisciplinary team. Below, we have suggested revisions to the covered indications and exclusions/limitations sections, consistent with recommendations we have previously made to Novitas, First Coast, Palmetto, CGS, NGS, and WPS.

Proposed Revision:
Covered Indications
Percutaneous vertebroplasty (PVP) and percutaneous vertebral augmentation (PVA or kyphoplasty) procedures will be considered medically reasonable and necessary in patients who have been clinically evaluated by a physician with expertise managing spine disorders (Orthopaedic Surgeon, Physiatrist, Neurosurgeon, Pain Management Specialist, etc.) for the following indications:

1. Painful, debilitating, osteoporotic vertebral collapse/compression fractures, defined as those that have not responded to non-surgical medical management (e.g., narcotic and/or non-narcotic medication, physical therapy modalities) with and without methods of immobility (e.g., rest, bracing).

    - Both PVP and PVA will be considered reasonable and necessary when ALL of the following criteria are met:
        - Acute to subacute osteoporotic VCF (T5 – L5) confirmed by recent (within 30 days) advanced imaging demonstrating bone marrow edema on MRI or bone-scan/SPECT/CT uptake[1-3,8,21] ; **and**
        - The beneficiary is symptomatic and is hospitalized with severe pain (Numeric Rating Scale [NRS] or Visual Analog Scale [VAS] pain score ≥ 8)[4-7] **or** is non-

hospitalized with moderate to severe pain (NRS or VAS ≥5) despite optimal non-surgical management (NSM)[8]**:**

- Worsening or persistent pain **<u>or</u>**
- Stable to improved pain (but NRS or VAS ≥5) **when 2 or more of the following are present:**
  - Progression of vertebral body height loss
  - > 25% vertebral body height reduction
  - Kyphotic deformity
  - Severe impact of VCF on daily functioning

2. Exclusion criteria:
   a. Absolute:
      i. Active infection at surgical site
      ii. Untreated blood borne infection
   b. Strong contraindication:
      i. Osteomyelitis
   c. Usually contraindicated:
      i. Pregnancy
   d. Relative Contraindications to perform vertebral augmentation alone:
      i. Allergy to fill material
      ii. Coagulopathy
      iii. Spinal instability
      iv. Myelopathy from the fracture
      v. Neurologic deficit
      vi. Neural impingement
      vii. Fracture retropulsion with neurologic compromise

As indicated in the attached letter signed by many organizations and also mentioned at the March 2019 Multijurisdictional Contractor Advisory Committee (CAC) meeting by various groups and stakeholders, sufficient literature is available to support vertebral augmentation for the patient population identified above. Limiting this procedure to fractures <6 weeks old should be revised or eliminated as this requirement will have a negative impact on patient outcomes and providers' ability to provide evidence-based and appropriate spine care to our patients.

Additionally, the MPW disagrees with requiring a consensus from a multidisciplinary team including four physicians. The MPW believes that this requirement is not established in the literature and will lead to increased costs and delays in patient care. For example, why does a neurologically intact patient with an acute painful osteoporotic vertebral compression fracture require consultation from a neurologist? Some data or information on the source of this restriction would be helpful.

We recommend removing the reference to the Roland Morris Disability Questionnaire as multiple valid tools that demonstrate functional disability exist. Our subject matter experts also recommend using exclusion criteria that further stratify the degree of contraindication

to allow for a more individualized approach to treatment in unusual circumstances. The relative contraindication regarding fracture retropulsion needs to be modified to include "with neurologic compromise" as vertebral augmentation can be carefully performed in patients with limited degrees of posterior vertebral wall involvement.

While periosteal infiltration remains a treatment option as part of nonoperative care, we do not believe the literature supports this as a required treatment prior to vertebral augmentation. Finally, based on our review it seems that the coverage benefits for this procedure seem to vary by each region. We are hopeful that an appropriate coverage decision can be crafted that allows for patients to have access to appropriate treatment regardless of their region/location across the country.

We hope that Noridian will consider our comments and revise this Local Coverage Determination to reflect all new evidence and provide coverage accordingly. We welcome the opportunity to further elaborate on the comments provided herein and look forward to working with you to improve patient access to care and outcomes.

If you have any questions or wish to discuss our comments, please contact Belinda Duszynski, Senior Director of Policy and Practice at the Spine Intervention Society at bduszynski@spineintervention.org.

Sincerely,

American Academy of Pain Medicine (AAPM)
American Academy of Physical Medicine and Rehabilitation (AAPMR)
American Association of Neurological Surgeons (AANS)
American College of Radiology (ACR)
American Society of Anesthesiologists (ASA)
American Society of Neuroradiology (ASNR)
American Society of Spine Radiology (ASSR)
Congress of Neurological Surgeons (CNS)
North American Neuromodulation Society (NANS)
North American Spine Society (NASS)
Society of Interventional Radiology (SIR)
Spine Intervention Society (SIS)

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 all 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
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Letter Supported by:

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North American Spine Society
American Society of Spine Radiology
North American Neuromodulation Society
American Society of Neuroradiology
International Society for the Advancement of Spine Surgery

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