

Spinal Injections - Re-review

**Draft Evidence Report:
Peer Review, Public Comment & Response**

February 12, 2016

Health Technology Assessment Program (HTA)

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Responses to Clinical And Peer Reviewers (Section 1, Table 1)**Responses to Public Comments** (Section 2, Table 2)

Spectrum Research is an independent vendor contracted to produce evidence assessment reports for the Washington HTA program. For transparency, all comments received during the public comment periods are included in this response document. Comments related to program decisions, process, or other matters not pertaining to the evidence report are acknowledged through inclusion only.

The first section responds to clinical and peer reviews received from the following parties:

Draft Report

- James R Babington, M.D., Medical Co-Director, Comprehensive Spine Program, Section of Physical Medicine and Rehabilitation, Pain Management, Virginia Mason Hospital & Seattle Medical Center
- Daryl, Fourney, M.D., Division of Neurosurgery, Royal University Hospital, Saskatoon, Saskatchewan, CANADA
- Pradeep Suri, M.D., M.S., Associate Professor, University of Washington, Department of Rehabilitation Medicine; Staff Physician, Division of Rehabilitation Care Services, VA Puget Sound Health Care System; Investigator, Seattle Epidemiologic Research and Information Center (ERIC), VA Puget Sound Health Care System

Specific responses pertaining to peer reviewer comments are included in Table 1.

Responses to public comment may be found in Table 2.

Full text of peer review and public comments follows in the Appendix.

Table 1. Responses to Clinical and Peer Reviewers

Comment	Response
Peer Review: James R. Babington, M.D.	
Introduction, Page 2, Policy Context	While the FDA did place warning labels on the use of epidural corticosteroid injections, this did not constitute a significant change from the known risks. The outcome of the working group convened by the US FDA Safe Use Initiative did make specific recommendations to mitigate the risk of rare, but well-recognized complications of epidural steroid injections (Benzon et al JAMA. 2015;313(17):1713-1714). Adherence to best practices can help improve the safety profile of any procedure, but is unlikely to “eradicate” it. Imaging guidance is recommended for all cervical spinal injections.
Introduction, Page 3, Population	Patients with subacute and chronic pain are part of the review. Is there a specific reason why patients with acute pain <4 weeks duration are excluded?
Background, general	Background accurately describes the scope of the problem. Unfortunately, the text suggests that spinal injections have a role in the treatment non-specific spine pain. It does not address the appropriate use of spinal injections. While non-specific low back pain does not have a high correlation with imaging findings as described in van Tulder et al (Spine 1997; 22: 427-434), this is not the patient population where injections should be employed. Appropriate use of injections, focuses on the treatment of patients with a history and physical exam that is supported by imaging findings. The inclusion of coverage policies from other carriers is helpful as are guidelines.
Report Objectives & Key Questions, page 32	Spinal injection procedures are not indicated for non-specific low back or neck pain. The disease and treatment paragraphs suggest that the use of spinal injections may be applied in that patient population. Spinal injections are a targeted treatment for specific spinal conditions within the context of a patient history and physical examination that is supported with concordant
	Noted, thank you.
	Acute pain was not within the scope as outlined by the State of Washington.
	Thank you for your comment. Some trials included in this technology assessment report on spinal injections for non-specific back pain. The intent of mentioning non-specific spinal pain in the background is to acknowledge that there are clinical trials of spinal injections on non-specific back pain. Furthermore, the diagnoses in clinical practice as well as in the clinical trials for this condition is not always accurate.
	Thank you for your clinical perspective. Please see response above.

Comment	Response
	<p>anatomic abnormalities on imaging studies. Spinal injections should be considered directed procedures aimed at treating a defined pathoanatomic etiology for pain.</p>
<p>Methods, page 78, Intervention</p>	<p>Although the analysis stratifies based on condition, there are instances where the condition is poorly defined in the primary paper. The etiology for the symptoms is key in fully understanding the response to any treatment. Combining multiple etiologies for the painful condition will lead to erroneous conclusions. Additionally, myriad technical approaches are employed and combined in the analysis for efficacy. For example, image guidance is used in some studies and not in others. Caudal, interlaminar, and transforaminal techniques are all combined in the analysis yet most practicing interventional spine would agree that there are vast differences between each. This is misleading in developing a determination for efficacy.</p>
<p>Methods, page 79, Study Design</p>	<p>The use of only RCT to determine the efficacy under KQ1 limits a comprehensive understanding of the literature. Medical science routinely uses RCTs to determine efficacy however there is a rich level of experience and knowledge that is obtained using other types of studies. To exclude them is limiting significant information that is routinely used to provide care to our patients. The observation of outcome particularly in an interventional/surgical area where randomization cannot easily be performed should not be discounted. Evidence based practice is the integration of best research evidence, clinical expertise, and patient’s values (Sackett DL, et al. BMJ 1996; 312:71-2). To be good stewards of our practice we need to ensure that inflexible rules do not produce care that is management driven and not patient centered (Greenhalgh T et al. BMJ 2014; 348: g3725).</p>
<p>Methods, page 80, section 3.1.3</p>	<p>Regarding literature search, it would be helpful to know which “reference lists of relevant studies” and “several systematic reviews” were used.</p>
	<p>Thank you for your comment.</p>
	<p>Thank you for your comments</p> <p>Well-conducted RCTs remain the standard for evaluating the efficacy of an intervention. Comparative observational studies with concurrent controls can be helpful in certain situations when the outcome is “hard” and quantitative, (e.g., evaluating death). However, they are susceptible to selection bias and confounding, and have been shown to overestimate the effectiveness of a treatment, especially one based on subjective outcomes. When ample RCTs are available, these studies are used to provide the highest level of evidence. When there is a lack of RCTs to provide evidence on efficacy, we look for comparative observational studies with concurrent controls as the next best level of evidence.</p>
	<p>The bibliographies of all included articles were reviewed as were those of the systematic reviews and HTAs listed</p>

Comment	Response
	in Tables 3 and 4 (Section 2.5). We have also updated the methods section to state this more clearly.
Methods, page 80, section 3.1.3	Stage three <i>a priori</i> inclusion criteria are not explicated.
Thank you for your comment. The Inclusion/exclusion criteria are spelled out in the section prior (3.1.2 on pages 78 and 79).	Methods, page 82, section 3.1.5
The determination of strength of evidence initially seems straight forward and to be based on the fact that the evidence results from a randomized controlled trial. However, it appears that the SoE can be up or downgraded based on a qualitative assessment of risk of bias, consistency, directness, precision, and publication bias. It is not entirely clear how those factors are objectively applied and weighted to influence the strength of evidence that is ultimately reported.	Appendix D details the criteria and the process used to determine risk of bias and overall strength of evidence. Detailed information on the risk of bias for each individual study can be found in Appendix E. The Appendix is published as a separate document. Further, the various SoE domains (with information regarding upgrading or downgrading) are now displayed in the summary tables in both the Executive Summary and Section 5 of the full report.
Methods, page 83, section 3.1.6	It is challenging to accept that the Weighted Mean Difference is an accurate estimate of outcome for pain when the interventions are significantly different in approach and medication delivered.
Most trials presented results on pain in terms of means. However, whenever possible we performed analysis on proportion of patients achieving either pain or function success as defined by the study authors (usually 50% improvement). Results were similar with either analysis.	Methods, page 83, section 3.1.6
Regarding, missing standard deviations were other methods for imputing missing data sought and did they yield a different result from using other studies to estimate the values?	No, we only used the method described in section 3.1.6 and did not do a sensitivity analysis of other methods.
Results, general	The detail presented is sufficient though it is an enormous challenge to address the entire field of spinal injections in a single report. The key questions are addressed though the conclusions do not reflect the current state of practice. There are no recommendations to address limitations in the literature rather conclusions are drawn based off of low quality primary studies.
Noted. The purpose of the review is to summarize the evidence, not to make clinical or policy recommendations.	Results, page 86, section
34 RCTs are assessed. The etiology includes foraminal stenosis and disc degeneration which	Thank you for your comment. We describe the patient populations and

Comment	Response			
4.1.2	are combined in assessment. Treatment included non-image guided, ultrasound guided, and fluoroscopically guided injections. Approaches spanned caudal, interlaminar and transforaminal techniques. Injectates included five different medications. This analysis does not reflect current practice standards and does not give appropriate data to draw relevant conclusions regarding efficacy.			
Results, page 92, section 4.1.4	Trials included a variety of etiologies for spinal stenosis. Only three studies required confirmation by MRI or CT scan for the presence of spinal stenosis. Again myriad treatments and techniques hamper the ability to make sound conclusions.			
Results, page 94, ESI vs. disc procedures	The MILD procedure is not a disc procedure. This procedure addresses hypertrophic ligamentum flavum via a percutaneous approach.			
Results, page 100, section 4.1.8	Epidural steroid injections are not indicated for the treatment of sacroiliac joint pain. It should read "sacroiliac joint injections" rather than "epidural steroid injections".			
Conclusions	The results of this analysis are not sufficient to detect differences between groups. The major challenges are absence of quality basic clinical evidence for these procedures using current techniques, neglect of other sources of information, and the heterogeneous nature of			
their diagnoses as they are reported in the studies. There was insufficient evidence from study descriptions to determine with certainty the cause of the radicular symptoms. With respect to approach, we stratified results by injection approach in all the major analyses. There were no clear and consistent differences in efficacy when trials were stratified by approach. There was insufficient evidence to determine effects of imaging guidance because all trials of transforaminal injections used imaging guidance while only a few trials employing other approaches used fluoroscopic guidance.	There were 10 trials of lumbar stenosis. Of these, eight required CT and/or MRI confirmation of stenosis. Six of the 10 trials contributed to the meta-analysis comparing ESI with control injections. Of these six, four required imaging confirmation. The only trials for which imaging confirmation was unclear were the two by Manchikanti et al. (Caudal 2012/2012/2008 and Interlaminar 2015/2012). We have corrected this error, both in the report and in the Appendix.	Thank you for your comment. We have updated our report to expand the comparison to disc or decompression procedure.	Thank you. We have made this change throughout the report.	Thank you for your comment. We describe the patient populations and their diagnoses as they are reported in the studies. There was insufficient evidence from study descriptions to determine with certainty the cause of

	Comment	Response
	diagnosis and treatment approaches. The more accurate assessment is that there is insufficient high quality RCT data to reach a definitive conclusion.	the radicular symptoms. With respect to approach, we stratified results by injection approach in all the major analyses. There were no clear and consistent differences in efficacy when trials were stratified by approach. There was insufficient evidence to determine effects of imaging guidance because all trials of transforaminal injections used imaging guidance while only a few trials employing other approaches used fluoroscopic guidance.
Conclusions	The only conclusion based on presumed high quality data was in the injections for the treatment of lumbar stenosis. Interestingly, although there is no difference in “pain success” or “function success” there was statistically significant improvement in both the treatment and control arms of the trial cited here. This suggests that patients did improve with spinal injection into the epidural space however there was no significant difference in pain or function between the steroid and local anesthetic group.	The comparison between treatments is the comparison of interest. Noting that both groups improved and concluding that it was the injection (with or without steroid) that caused the change is unwarranted, and fails to consider that subjective improvement in patients may result from factors other than the injection procedure. Some of these factors include the natural course of the condition, the effects of placebo, and measurement error.
Overall Presentation and Relevancy	The report is well structured and organized. Main points are clearly presented. The focus and use of only RCTs belies current practice. The report emphasizes the rapid increase and overuse of spinal injections while suggesting there is little good evidence for injections in the treatment of spine pain. The assessment of appropriate use of spinal injections is important for public policy, however the conclusions drawn erroneously suggest that spinal injections are not relevant in this treatment arena. Other well performed studies have come to vastly different conclusions than this report. Clinical experience in well-selected patients suggests that this is a treatment approach that provides significant benefit to patients who have few other therapeutic options and may be reasonable when used appropriately.	This report is consistent with the AHRQ report published in 2015 and the well done systematic review by Pinto et al. 2012. Also, please see Tables 3 and 4 which outline these and other various systematic reviews and Health Technology Assessments.
Quality of Report	Fair	Thank you.

Comment	Response	
<i>Peer Review: Daryl Fourney, M.D.</i>		
Introduction, general	The introduction provides an overview of the topic and highlights the increasing use (and therefore cost) of spinal injections to treat neck and back related pain, especially when there are significant concerns about the efficacy and safety of these procedures	Thank you for your comment.
Background, general	The content of background information is sufficient. The background raises the points about new safety concerns from the FDA, and new literature that addresses safety and (particularly long term) effectiveness. Here is an overview of the types of procedures, the mechanism of action. Published guidelines are reviewed as well as previous systematic reviews. Finally, there is an overview of Medicare and private insurance coverage policies.	Thank you for your comment.
Report Objectives & Key Questions, general	Objective was to update previous review. The key questions address all relevant questions regarding safety and effectiveness, including analysis of patient sub-populations which may or may not benefit from the intervention, the type of intervention and the provider. As well direct and comparative costs are questioned	Thank you for your comment.
Methods, general	The inclusion/exclusion criteria for studies is succinctly outlined in Table 6. New publications were searched from 2010-2015 to supplement the previous review. After exclusions, there were 120 new articles included. The strength of evidence for studies was assessed using standards as outlined on page 82. The method used is consistent with the latest principles in evidence-based medicine and has been accepted in multiple peer-reviewed systematic reviews by the authors. Strength of evidence for economic studies is problematic, as outlined by the authors on page 82, because standardized methods for determining the strength of evidence for these studies is not generally accepted. This affects key question 4. Overall, the data abstraction method was very rigorous and standardized.	Thank you for your comment.
Results, general	There is a tremendous amount of detail provided, but the authors have done a great job	Thank you for your comment.

Comment	Response	
	<p>summarizing it in table form. A large number of tables is required given the multitude of comparisons for different techniques and length of follow-up. The strength of evidence is listed for each outcome assessed. The authors have presented the conclusions in an unbiased manner. There is very little published in terms of cost effectiveness data, and the authors have summarized this well (page 147).</p>	
Conclusions, general	<p>The conclusions stated for individual studies appears fair and unbiased. There are no overall conclusions for policy based on the results of the review.</p>	<p>Thank you for your comment.</p>
Overall Presentation & Relevancy	<p>This is a very detailed, well written review encompassing all relevant clinical and cost-related factors pertaining to therapeutic spinal injections. Points are presented in a clear unbiased fashion. Due to multiple comparison studies using different techniques and follow-up time, there are a large number of tables, but a certain level of granularity is required so that different studies are not lumped together inappropriately. I think that the authors have achieved a good balance here. This type of critical analysis is very important for public policy given the growing burden of chronic pain in society and the associated costs of treatments which may or may not be appropriate.</p>	<p>Thank you for your comment.</p>
Quality of Report	<p>Superior.</p>	<p>Thank you.</p>
From an email sent separately	<p>In looking over your appendix, I noted that you missed some relevant studies that should be considered in the data set:</p> <ol style="list-style-type: none"> 1. Ghareman, A et al. The efficacy of transforaminal injection of steroids for the treatment of lumbar radicular pain. <i>Pain Medicine</i> 2010; 11: 1149-1168. - I see it in the citation list as included (#86) but don't see where it shows up in the tables. 2. Vad, V et al. Transforaminal epidural steroid injection in lumbosacral radiculopathy: a 	<p>See answers that correspond to the numbered comments below:</p> <ol style="list-style-type: none"> 1. It is there – see Appendix pages 15, 31, 72, 107, 248, 261, 312, and 316. Note that the spelling is Ghahreman. 2. Vad et al was excluded at review of title/abstract because it was not a randomized trial. Though the Vad et al study describes itself as a RCT, its methods state that

Comment		Response
	<p>prospective randomized study. Spine 2002; 27(1): 11-15.</p> <ul style="list-style-type: none"> - Doesn't look like it was reviewed or excluded. <p>3. Kennedy DJ et al. Comparative effectiveness of lumbar transforaminal epidural steroid injections with particulate versus nonparticulate corticosteroids for lumbar radicular pain due to intervertebral disc herniation: a prospective randomized double-blind trial. Pain Medicine 2014; 15: 548-555.</p> <ul style="list-style-type: none"> - Comparative effectiveness trial that shows improvement in both groups, but no significant difference except in number of injections in nonparticulate group <p>4. MacVicar J et al. The effectiveness of lumbar transforaminal injection of steroids: a comprehensive review with systematic analysis of the published data. Pain Medicine 2013; 14: 14-28.</p> <ul style="list-style-type: none"> - Useful literature review 	<p>patients were assigned to treatment by patient choice ("randomized by patient choice"). Consequently, this study was not randomized and therefore excluded.</p> <p>3. We did not evaluate articles comparing types of steroids (non-particulate vs. particulate) with respect to effectiveness. We did look at the safety of particulate/non-particulate steroids, but no safety data were presented in this article (Kennedy DJ et al.).</p> <p>4. MacVicar et al. was not a systematic review; rather it was a narrative review with no stated inclusion/exclusion criteria. They included a sampling of RCTs, cohort studies and case series.</p>
<p>Peer Review: Pradeep Suri, M.D., M.S.</p>		
	Specific comments	
Introduction, general	The overview is generally very thorough and certainly adequate. The topic of the assessment is important, and the clinical and policy relevance are well defined.	Thank you.
Introduction, page 1	Regarding the sentence, "In general, spinal injections are indicated for average pain levels greater than 6 on scale of 0–10; intermittent or continuous pain causing functional disability; or chronic pain that has failed to respond to more conservative therapies.", there is no universally accepted cutoff for what level of pain on a NRS or VAS is sufficient to warrant spine injections. I would recommend this cut-off off 7/10 be removed, or stated as specific to the sources cited with qualification that there is no widely accepted cutoff. This cutoff for pain is also mentioned on page 49- "In general, epidural, facet joint, and	Thank you. After review, we agree that this statement was included erroneously; it has been removed from the report in both places cited.

Comment	Response
	sacroiliac joint injections are indicated for average pain levels greater than 6 on scale of 0–10”.
Introduction page 44	2 nd paragraph from bottom of page- the word ‘face’ is written instead of ‘facet’
Introduction, page 50, section 2.2.5	<p>In this section it might also be mentioned that there is an opinion among many clinicians that particulate steroids have greater positive effects than non-particulate steroids (although not necessarily with clear evidence supporting this view). It is also held that the issue of particulate vs. non-particulate steroids (and the greater risk of particulate steroids for catastrophic AEs) is greater with transforaminal epidurals, and is either not present or is much lower with interlaminar epidurals.</p>
Background, general	The literature review and background is sufficient, and clearly written.
Background, page 45	<p>I would recommend using alternate terminology to replace the dated term ‘degenerative disc disease’, which has been out of favor for some time due to the near-ubiquitous nature of disc degeneration in middle to older age adults. The terminology ‘disease’ alone can be damaging for patients to hear, and can reinforce illness conviction and maladaptive pain beliefs. I would recommend if possible to use the less polarized term ‘disc degeneration’ as a substitute and to list ‘disc degeneration’ as a synonym if needed, or at a minimum to acknowledge the limitations of the term ‘degenerative disc disease’.</p>
Background, page 47	<p>The epidural procedure descriptions on this page underlie the conceptual rationale for why the results of RCTs pertaining to these fundamentally different procedures (ESI IL vs TF vs. caudal) should not be pooled together in a meta-analysis. See further comments on this below.</p>

Comment	Response	
Report Objectives and Key Questions	The aims and questions clearly address relevant policy and clinical issues, although some, such as key question 3, seem well beyond the current state of the scientific literature. The key questions are clearly defined.	Thank you.
Methods, general	The method for identifying relevant studies is rigorous in terms of the literature search, evaluation of study quality, study characteristics, and study risk of bias. The reviewers should provide an explanation for why acute radicular pain <4 weeks was a study exclusion criteria, since ESIs are sometimes done for intractable acute radicular pain, especially when pain is very severe and the only other option is surgery.	Thank you for your comment. Acute pain was not within the scope as outlined by the State of Washington.
Methods, general	The methods for LOE are appropriate and clearly explained.	Thank you.
Methods, general	<p>The data abstraction and analysis review are generally adequate. However, various important clinical criteria were not accounted for in terms of classifying studies. In particular, various different types of interventions were pooled together in a manner that I believe to be inappropriate based on clinical/conceptual reasons.</p> <p>The review in various locations comments on differences with respect to injection approaches for ESI (such as TF vs. IL vs. caudal, pp 47-51), the separation of fluoroscopic vs. non-fluoro guided procedures, and control groups (e.g. ENSI vs. NEI), which highlights very important conceptual and technical distinctions between these procedures. However, these distinctions were largely ignored in the results summary/meta-analysis, and groups were simply pooled with respect to these various subgroups.</p>	Thank you for your comment. Please see responses to the specific subgroups mentioned in the next three answers.
Methods, general	Regarding injection approach: the 3 major ESI procedures in the review (TF vs. IL vs. caudal) are quite different from one another technically, as is described in the document, and in my opinion there is no compelling conceptual reason why one should pool the results of these different procedures. They are different procedures. The risk factor profiles for the different ESI	We stratified results by injection approach in all the major analyses such that subgroup analyses are provided for the different injection approaches. There were no clear and consistent differences in efficacy when trials were stratified.

Comment	Response
	<p>approaches are also conceptually different, based on anatomic considerations. For instance, TF ESIs (with particulate steroid) are most commonly the procedure type implicated in the rare occurrence of catastrophic ESI-related AEs resulting in paralysis, with substantially lower risks for these types of catastrophic AEs in IL or caudal ESIs. These conceptual reasons underscore why the results should be presented separately via approach, and not pooled in the texts, figures and/or tables.</p>
Methods, general	<p>Regarding fluoroscopic guidance: the lack of fluoro guidance for a specific trial means that such a trial did not and could not confirm that steroid was actually placed in the epidural space. All of these trials without fluoro guidance could therefore result in some misclassification of the intervention itself (is actually steroid placed in the epidural space?), and bias towards a null result for those trials. The necessity for fluoro guidance is underscored by the 2015 US FDA guidelines to prevent neurologic complications that is described on pp. 57-58 (“Safeguards to Prevent Neurologic Complications after Epidural Steroid Injections (2015”).</p>
Methods, general	<p>Thank you for your comment. Use of fluoroscopic guidance in each trial was labeled in the meta-analyses figures; one can visually inspect the results between those trials with fluoroscopy and those without. All the trials of transforaminal injections used imaging guidance and these results are presented together in the stratified analysis. There was insufficient evidence to determine effects of imaging guidance because all trials of transforaminal injections used imaging guidance and few trials of other approaches used imaging guidance. However, there were no clear differences in effectiveness when trials were stratified by the approach used (as stated above).</p>
Methods, general	<p>Thank you for this comment. Interpretation of indirect comparisons are fraught with difficulty and must be made with caution. There are 3 studies that directly compare ENSI with NEI for short term pain and function, and risk of surgery. The two control groups are nearly identical in all outcomes. We have added this comparison in Appendix BB.</p>

Comment	Response
	<p>and calculates an indirect comparison of ENSI vs. NEI that is suggestive of real differences (albeit such differences were not seen in the 2 studies illustrating direct comparisons).</p>
<p>Methods, general</p>	<p>A distinction not commented on is the combining of anesthetic control injections and saline/water (without anesthetic) control injections into one control group. For TF epidural injections of anesthetic, and also for IL epidural injections of anesthetic to a lesser degree, patients with lumbosacral (LS) radicular pain will often be able to discern when they have an epidural with anesthetic, because an anesthetic-only epidural will temporarily block radicular pain corresponding with a specific nerve root, depending on the placement of the injection. For instance, a TF epidural injection of anesthetic (without steroid) is very similar to a ‘selective nerve root block’ (SNRB). In an SNRB, the disappearance or relief of typical radicular pain indicates the specific nerve root level of pain. This would have differential effects on blinding with a TF epidural with anesthetic, as compared to a TF epidural performed with saline. This argues against pooling the results of studies using these two types of control injections, at least with respect to very short-term outcomes. In addition, there are many clinicians who believe that anesthetic injections into the epidural space- and elsewhere- can have therapeutic benefits beyond the usual expected duration of anesthetic effects, and beyond that seen with epidural saline, albeit very short term.</p>
	<p>Thank you for your comment. We understand the theoretical basis for this argument. However, the data from the included studies do not support this line of reasoning. For example, there was no combining of controls in the studies using the caudal or interlaminar approaches in patients with radiculopathy due to disc pathology and or foraminal narrowing. All of these studies comparing epidural steroid plus anesthetic injection used an anesthetic injection as the control. In studies comparing epidural steroid plus anesthetic injection using the transforaminal approach, one study included a saline control and an anesthetic control (Ghahreman). The study found no difference in the response between the saline and anesthetic control. In fact, the saline control had a higher proportion of patients achieve relief of pain at 1 month compared with the anesthetic group, though this was not statistically significant (19% vs. 7%). This result would argue against the idea that an anesthetic control group may benefit from a differential effect as a result of the loss of blinding.</p> <p>There were four additional studies using the transforaminal approach: three used anesthetic with or without saline as the epidural control (Tafazal 2009, Cohen 2012, Manchikanti 2014) and one used saline alone as the control epidural injection (Karppinen). The one using saline alone reported no difference in mean pain scores compared with the epidural steroid plus anesthetic, mean difference 0.12</p>

Comment	Response	
	(95% CI: -0.32, 0.56) on a 10-point pain scale. Again, there is no evidence that the effect of a control epidural injection with anesthetic is different than a control epidural injection without anesthetic. Therefore we felt justified in combining the results of studies when the epidural injection control had either saline alone or anesthetic with or without saline.	
Methods, general	<p>Another important issue is the time frame of follow-up used in the review. The shortest-term follow-up duration included in the review is ≤ 3 months. This obscures our understanding of what happens in the very short term (≤ 1 month) after these procedures. This is particularly important since the duration of effect for these procedures is often very short (often ≤ 1 month), and the treatment effect would be expected to have mostly disappeared by 3 months. Not registering what happens in the very short term is part of what creates this chasm between what clinicians/patients observe in the immediate/very short-term, and what clinical studies pick up when the first follow-up assessment is at a 3-12 month time frames. I would recommend a separation out of immediate/very short-term results (≤ 1 month) from short-term results (2-3 months).</p>	<p>Thank you for your comment. We chose the 3 month cut-off to be consistent with the original report and added a >12 month long-term period to accommodate the growing body of follow-up literature. It is acknowledged that if there is any benefit from spinal injections for radiculopathy due to disc pathology or foraminal narrowing, it is in the short-term as demonstrated by our results (i.e., pain success); those from the Pinto systematic review (summarized in Table 3 of the report); and those from the health technology assessment by Chou (summarized in Table 4 of the report). However, in all reports, the improvements were small relative to the comparison groups and less than the proposed threshold for clinically important change.</p>
Methods, general	<p>My comments as above pertain to the 'Efficacy Results' and Table 1 beginning on page 5, and also pertain to figures 3-22 and their corresponding tables. Of note, statistical explanations for why pooling is or is not justified are irrelevant due to the conceptual reasons stated. To my knowledge, statistical methods such as heterogeneity testing, subgroup interactions, and the profile likelihood method cannot address the conceptual problems with pooling distinct procedural categories. I'd recommend that the results be presented separately by approach, with or without fluoro guidance, etc.</p>	<p>Thank you for your comment. Please see comments above with respect to approach, procedure categories and fluoroscopy.</p>
Results,	In general, the level of detail was excellent with	Thank you.

Comment	Response
general	the extensive results section. It is clear that meticulous attention has been paid to many aspects of the lit search, data collection, and extraction.
Results, general	I can't find clear statements regarding answers regarding 2 aspects of the 4 key questions. For instance, I wasn't able to find the conclusions regarding efficacy related to repeated spinal injections, multilevel spinal injections, and bilateral vs. unilateral spinal injections (key question 1). I also can't find any statement regarding conclusions pertaining to treatment modifiers by steroid particulate size (key question 3, page 77).
Results, page 84	Thank you for identifying this omission. We found no evidence that directly addressed these issues. The following was added to reflect this: Section 4.1.16: Many studies included repeat, multilevel, and bilateral injections. However, like the previous review, we did not find any studies that compared repeat with single injections, multilevel with one-level injections, or bilateral with unilateral spinal injections. Section 4.3.1 at the end: We found no studies evaluating the differential efficacy and safety comparing steroid particulate size.
Results, page 87	Regarding the sentences: "We assessed the presence of statistical heterogeneity among the studies by using the standard Cochran's chi-square test, and the magnitude of heterogeneity by using the I^2 statistic. When statistical heterogeneity was present, we performed sensitivity analyses by omitting obvious outliers, and by conducting meta-analysis using the profile likelihood method" I do not specialize in conducting meta-analyses, however, to my understanding the I^2 statistics seem high throughout many of the meta-analyses from the various figures. Outlier omission was only done 2 or 3 times that I saw in the report. More detail regarding how heterogeneity was assessed and/or dealt with would seem important in light of the high I^2 s. Also, the testing of the subgroup interactions was not described.
	When there was a large amount of statistical heterogeneity, we first looked to see if there were any obvious outliers. If so, we repeated the analysis excluding the outlier and compared the results. In cases where there were no obvious outlier, we repeated the analysis excluding poor quality studies. When an analysis only contained high quality studies, we did sensitivity analysis using the profile likelihood method and compared results. All sensitivity analyses yielded similar conclusions to that of the primary analyses and thus were not reported further. We clarified this method in the methods section on page 84.
	Thank you for your comment. It is true that very few of the studies using the IL and caudal approaches used image guidance. On the other hand, all of the studies reporting transforaminal

Comment	Response
	<p>space. All of these trials could result in some misclassification of the intervention itself, and bias towards a null finding.</p>
<p>Results, page 87</p>	<p>injections did so. As a result, there was insufficient evidence to determine effects of imaging guidance. However, there were no clear differences in effectiveness when trials were stratified by the approach, transforaminal versus other approaches.</p>
<p>Results, page 87-88</p>	<p>Regarding the following sentence: ‘Pain Improvement from Baseline’- “There was no difference between epidural steroid injections and epidural non-steroid injections with anesthetic and or saline/water with respect to improvement in pain scores at short-term (Figure 3, 15 trials, mean difference -0.46 (95% CI: -0.97, 0.05)”.</p> <p>However, Figure 3 lists comparison groups including both ENSI <u>and</u> NEIs, in contrast to the quoted statement. I believe the same misstatement is made for other of the following sentences from the paragraphs on p87-88 as well, corresponding to Figure 5, Figure 6, Figure 8, Figure 9, Figure 11, Figure 12, Figure 14, Figure 17, and so on.</p>
<p>Results, page 92</p>	<p>The summary descriptions reference the Figures, but should also probably reference the appropriate Tables from p163-280.</p>
<p>Results, page 92</p>	<p>Thank you for this observation. We have corrected these to read “...between epidural steroid injections and control injections” throughout.</p>
<p>Results, page 92</p>	<p>Regarding the sentence: “Patients were included if they had chronic function-limiting back and/or leg pain or signs of neurogenic claudication; MRI or CT confirmation of spinal stenosis was required in three studies.”</p> <p>If only 3 studies had MRI or CT confirmation of spinal stenosis, the other studies are not actually studies of interventions for symptomatic lumbar spinal stenosis or lumbar spinal stenosis (it cannot be known if patients have actual lumbar spinal stenosis without MRI/CT/CT myelogram or myelogram). They may be studies of claudication or claudicatory-type pain, but cross-sectional imaging is a sine qua non for diagnosis for lumbar spinal stenosis or symptomatic lumbar spinal</p>
<p>Results, page 92</p>	<p>The appropriate tables have been referenced for the final report.</p>
<p>Results, page 92</p>	<p>After re-reviewing the inclusion criteria for these study we found that 8/10 did require CT and/or MRI confirmation of stenosis. The only trials for which imaging was unclear were the two by Manchikanti et al. (Caudal 2012/2012/2008 and Interlaminar 2015/2012). We have corrected this error, both in the report and in the Appendix.</p>

Comment	Response
	stenosis.
Results, page 92	<p>Regarding the sentences: “Due to the large amount of heterogeneity ($I^2=55\%$), we excluded one outlier trial (mean difference -0.81 compared with all others ranging from -0.20, 0.30). Excluding the outlier trial decreased statistical heterogeneity, ($I^2=0\%$), reduced the overall point estimate, mean difference 0.08 (95% CI: -0.12, 0.28) but did not change the overall results.”</p> <p>In Figure 18, the total heterogeneity appears to be listed as $I^2=74\%$, not 55%. If this exclusion of outliers was done based on heterogeneity, it is unclear why similar checks for the reasons underlying high total heterogeneity were not done for other of the metaanalyses/figures featured, given high I^2s such as Figure 3 ($I^2=97\%$), Figure 4 (98%), Figure 5 (90%), and other figures up to Figure 21.</p>
Results, page 92	<p>4/10 of the ‘LSS’ trials did not use fluoroscopic guidance, and for 2/10 the use of fluoro was unclear. These trials did not and could not confirm that steroid was placed in the epidural space.</p>
Results, Strength of	<p>Table 1 and Table 2- for the final version of these tables, it would be extremely helpful to cite the</p>
	<p>When there was a large amount of statistical heterogeneity, we first looked to see if there were any obvious outliers. If so, we repeated the analysis excluding the outlier and compared the results. In cases where there were no obvious outlier, we repeated the analysis excluding poor quality studies. When an analysis only contained high quality studies, we did sensitivity analysis using the profile likelihood method and compared results. All sensitivity analyses yielded similar conclusions to that of the primary analyses and thus were not reported further.</p> <p>We clarified this method in the methods section on page 84.</p>
	<p>Thank you for your comment. Of the 10 trials evaluating ESI in lumbar spinal stenosis, ESI was compared with a control injection (n=7: Cuckler 1985, el Zahaar 1991, Friedly 2014, Fukasaki 1998, Manchikanti 2012 & 2015 [interlaminar], Manchikanti 2008 & 2012 [caudal], Nam 2011); a decompression procedure (n=1: Brown 2012), conservative care (n=1: Koc 2009) and etanercept (n=1: Ohtori 2012). Of the seven comparing ESI with control injections, six contributed to the meta-analysis (Fukasaki did not as this trial only evaluated walking as an outcome). Of the six contributing to the meta-analysis, four used fluoroscopic guidance and two did not (Cuckler and el Zahaar). Both Cuckler and el Zahaar only contributed to long-term pain and surgery outcomes. There was no evidence that outcome was effected by fluoroscopic guidance.</p>
	<p>The study citations have been added to the Strength of Evidence Summary</p>

Comment	Response
<p>Evidence Summary Tables</p>	<p>publications (citation numbers) in the actual table so they can be more easily looked up. In the current form, it is impossible to quickly check the details of what is in the table without spending hours going back and forth to various parts of the document.</p> <p>Table 1, page 7: for the study cited as “No difference between ESI and posterior ligament injection of saline + oral gabapentin in pain or function, or the likelihood of achieving pain success”: I believe this is referring to the BMJ 2015 Cohen trial of ESI vs. gabapentin. This should mention that the ESI intervention also involved oral placebo pills as part of the intervention.</p> <p>For those interventions including ‘extra-articular’ injections, it would be good to clarify where in the extraspinal structures these injections were placed, even if as a table footnote.</p> <p>Table 2 p 17: One of the rows under “Facet pain: IASI versus Intra-articular control injection” lists “More improvement in pain with ESI versus ENSI.” I believe this was meant to state ‘more improvement with intrarticular steroid than with intraarticular nonsteroid</p> <p>Table 3- Due to the conceptual distinction of AE risk according to the ESI approaches (TF vs. IL vs. caudal), it would be useful to have the Table 3 FDA AE reporting database events stratified by injection approach. This is most pertinent because the catastrophic AEs related to particulate steroid use are believed to be most pertinent to transforaminal ESIs, and more rarely a consideration in IL and caudal ESIs (although to my knowledge all ESI types have had case reports of catastrophic AEs).</p> <p>Regarding the cost-effectiveness results: these are very clearly described, however the description of Arden/Price 2006 should likely state explicitly in the Executive Summary and</p>

Comment	Response
	<p>Results sections that the trial did not use fluoroscopic guidance, which might have efficacy and cost implications.</p>
<p>Results, page 108</p>	<p>Thank you for your comment. Information regarding use of imaging guidance has been added to both the SoE tables and results sections for all three included economic studies.</p>
<p>Results, page 108</p>	<p>There is a minor typo: "in one tria135,136l and".</p> <p>Thank you. We have corrected this error.</p>
<p>Results, page 108</p>	<p>There are several citation issues on this page.</p> <p>Thank you. We have corrected these errors.</p>
<p>Results, pages 163-280</p>	<p>Tables 8 to 75 – It would be easier to navigate these tables if citation numbers were added so the reader can quickly ascertain what study is being referred to (there are many studies by the same authors, for some of the authors listed in the reference lists). This issue also pertains to the earlier Tables, including Tables 1 and 2.</p> <p>Due to the similarity in the citations for trials conducted by Manchikanti, et al., we have cited these studies at the bottom of each corresponding table. For the other trials, they are easily found by name in the reference list, which is in alphabetical order. Regarding the Strength of Evidence Tables, the citation numbers have been added to all tables in both the Executive Summary and the Full Report.</p>
<p>Conclusions</p>	<p>Please see my comments above. This review was conducted with impeccable quality covering a vast range of the pain interventional literature. However, as stated above, based on conceptual grounds I do not believe that the 3 different epidural approaches are comparable sufficient to allow pooling of data, nor is pooling of non-fluoro guided interventions and fluoro-guided interventions. . Also, the combining of all outcomes <3 months seems inappropriate given that the expected duration of effect of ESI is likely substantially shorter for most patients. These issues is enough for me to question the validity of some of the efficacy-centered conclusions related to key question #1, including those pertinent to figures 3-29. That concern would be nullified if the results were broken out along the lines of ESI approach and fluoro guidance</p> <p>The conclusions regarding key question #2 are</p> <p>Thank you for your assessment. Please see the responses above with respect to the comments about approaches, image guidance</p>

Comment	Response
	<p>valid, but should be separated by epidural type to have actual clinical or policy relevance</p> <p>The conclusions for key questions #3 and #4 were largely not affected by pooling and are valid.</p>
Overall Presentation & Relevancy	<p>The review is well structured and organized, and summarizes a tremendous amount of data concisely. It is relevant to clinical medicine and has policy indications. However, in the effort to distill much data into concise messages, too much combining of distinct procedural types has occurred, per my descriptions above. I believe this could be remedied by the simple suggestions described above, separating out various aspects of the data which have now been combined. From what I have seen reported here, this would likely <u>not</u> result in conclusions which are different for the overwhelming number of comparisons made, but those conclusions may be more valid.</p>
Quality	<p>I would rate this report as superior regarding the technical and methodologic aspects of the review itself, excepting the decisions made with respect to pooling data for different procedures and with/without fluoro guidance.</p>

Responses To Public Comments

Spectrum Research is an independent vendor contracted to produce evidence assessment reports for the Washington HTA program. For transparency, all comments received during the public comment periods are included in this response document. Comments related to program decisions, process, or other matters not pertaining to the evidence report are acknowledged through inclusion only.

This section responds to public comments from the following parties:

Draft Report

1. Gary Franklin, M.D., Office of the Medical Director, WA State Department of Labor and Industries
2. Judith A. Turner, Ph.D., Janna Friedly, M.D., Bryan Comstock, M.S., Jeffrey G. Jarvik, M.D., M.P.H., University of Washington
3. Steven R. Pollei, M.D., Medical Director, Center for Diagnostic Imaging, Federal Way and Lakewood, WA
4. Brandon Messerli, D.O., EvergreenHealth, Kirkland, WA; and on behalf of a Multi-society Pain Workgroup
5. Belinda Duszynski, Senior Director or Policy and Practice, Spine Intervention Society, on behalf of a multisociety (15) review committee

Specific responses pertaining to comments are included in Table 2.

Table 2. Response To Public Comments Received

Comment		Response
Gary Franklin, M.D., Office of the Medical Director, WA State Department of Labor and Industries		
Page 5. Table 1.	The strength of evidence of most of RCTs was downgraded to “low” or “insufficient”. It would be helpful to provide some specific information about quality of the RCTs to justify the rating.	Appendix D details the criteria and the process used to determine risk of bias and overall strength of evidence (SOE). Detailed information on the risk of bias for each individual study can be found in Appendix E. The Appendix is published as a separate document. Further, the various SoE domains (with information regarding upgrading or downgrading) are now displayed in the summary tables in both the Executive Summary and Section 5 of the full report.
Page 78.	It may not be appropriate to group and pool the studies with different control injections (different substances), because the effect of an anesthetic injected into	Thank you for your comment. With respect to the epidural steroid intervention for radiculopathy due to disc pathology and or foraminal narrowing, 10 of the 11 studies in

Comment	Response
	<p>the epidural space, for example, is different from that of saline/water at least in a short term. The conclusion of a meta-analysis could be different if the substance in the control injections in the studies changes. In the meta-analysis on page 87 and Figure 6, the substances in the control injections were anesthetic and or saline/water, dry needling. It was concluded that “a greater proportion of patients receiving epidural steroid injections compared with epidural non-steroid injections (ENSI) with anesthetic and or saline/water achieved short-term successful pain relief defined as $\geq 20\%$, $\geq 50\%$ or 100% pain reduction (Figure 6), 11 trials, RR 1.30 (95% CI: 1.06, 1.58)”. Readers are not able to find out easily what control substance was used in each study from Figure 6 or the text. In addition, in the above meta-analysis, ESI in some studies contained not only steroid but also an anesthetic (e.g., Cohen et al., 2012; Ghahreman et al, 2010; Manchikanti et al. 2012). This makes the matter even more complicated. The way of grouping comparators (control injections) makes it very difficult to draw appropriate conclusions. I wonder if you can separate the studies with different experimental injections (steroid alone or steroid + anesthetic) and different control injections (saline/water or anesthetic) in your meta-analysis.</p>
<p>Page 107.</p>	<p>“Details on studies excluded after full text review are available in the Appendix C”. But Appendix C is not found in the document.</p>
<p>Page 281-299, Figures 3-24.</p>	<p>The labels of “Favors ESI” and “Favors Control” in the Forest plots are very helpful. However, the placement of the labels in the plots is not consistent. For</p>
	<p>Fig 6 administered anesthetic with the steroid. Dilke et al was the only study that administered steroid without anesthetic. They used an interlaminar approach and compared it with a control injection of saline alone into the interspinous ligament. We repeated the analysis in Fig 6 leaving out Dilke and this did not change the results.</p> <p>In the remaining 10 studies in Fig 6, one study (Ghahreman 2010) used a transforaminal approach and included a saline control and an anesthetic control. This study found no difference in the response between the saline and anesthetic control in a direct comparison. The remaining nine studies all used control injections with anesthetic.</p> <p>To explore the question concerning the effect of a control injection with and without anesthetic, we conducted an additional analysis on short-term pain and function stratified by the presence and absence of an anesthetic in the control injection group (see Appendix BB). There was no statistical difference between the control groups with and without anesthetic, though the epidural steroid group fared better against the anesthetic group than the saline group. These results (direct and indirect) would argue against the idea that there is a differential effect between an anesthetic control injection and a non-anesthetic control injection. Therefore we felt justified in combining the results of studies both in Fig 6 and elsewhere when the epidural injection control had either saline alone or anesthetic with or without saline.</p>
<p>The Appendix is published as a separate document.</p>	
<p>Our calculations consistently used the control as the referent group. For continuous variables, we subtracted the improvement in the treatment group from the improvement in</p>	

Comment	Response
	<p>example, “Favors ESI” is on the left side of the plot in Figure 11, but it is on the right in Figure 12. It would be helpful to rearrange the Forest plots so that “Favors ESI” is either on the left or the right side throughout the report.</p>
<p>the control group. In the case where the treatment group improved more, the effect size was negative (to the left side of the plot). For proportions, we calculated the relative risk. In the case where the treatment group improved more, the effect size was greater than 1 (to the right side of the plot). While the figure labels are not consistently on one side, we were consistent with keeping the control group as the referent group. This is also consistent with the AHRQ report (2015).</p>	<p>Judith A. Turner, Ph.D., Janna Friedly, M.D., Bryan Comstock, M.S., Jeffrey G. Jarvik, M.D., M.P.H., University of Washington</p>
<p>Executive Summary, Table 4</p>	<p>We recommend adding a citation for each study listed in the table.</p>
<p>Thank you for your suggestion. We have added citation numbers for all studies listed in the Strength of Evidence Tables.</p>	<p>Executive Summary, Table 4</p> <p>It is unclear to which study/studies the Table 4 footnotes 1 and 2 refer. We believe that the Table 4 footnotes would be more helpful if they were clearly linked to the relevant individual studies and more specific in terms of the issues relevant to bias in addressing the question of whether epidural corticosteroid injections are differentially effective for specific patient subgroups.</p>
<p>Thank you for your comment. The full version of the Strength of Evidence tables are now included in the Executive Summary. These tables include the domains evaluated (risk of bias, inconsistency, indirectness, imprecision) and whether the evidence was upgraded or downgraded based on each. Footnotes are used to provide explanations for up- or downgrading evidence which deviate from the standard 6 reasons presented just prior to the tables. Footnotes 1 and 2 will correspond to ratings in one of these cells. Also, citation numbers have been included for all studies listed in these Tables.</p>	<p>Executive Summary, Table 4, lumbar stenosis: ESI vs. control injections</p> <p>In our study (summarized in Table 4; Turner, J., Comstock, B., Standaert, C., Heagerty, P., Jarvik, J., Deyo, R., Wasan, A., Nedeljkovic, S., Friedly, J.: Can patient characteristics predict benefit from epidural corticosteroid injections for lumbar spinal stenosis? The Spine Journal, 15:2319-2331, 2015), we intentionally examined a large number (21) of potential predictors and multiple (6) outcomes because we wanted to be exhaustive and comprehensive in our search. We did not find that any baseline patient</p>
<p>Thank you for your comment. The criteria by which we evaluated risk of bias for studies evaluating heterogeneity of treatment effect were based on an Oxman and Guyatt article (as referenced in the methods; reference copied below) and were developed a priori. For credit, we looked for studies that evaluated a small number of subgroups specified a priori, and that provided a hypothesized direction of effect on all subgroups being evaluated. Studies that meet these criteria generally are testing hypotheses regarding specific subgroups rather than</p>	

Comment	Response
	<p>characteristic consistently predicted differential response to epidural injections of corticosteroid plus lidocaine versus lidocaine only. We agree that caution is warranted in making conclusions about a single predictor that is found to be statistically significant when a large number of statistical tests are performed, given that significant relationships could be found by chance in this situation. Had we concluded that a baseline patient characteristic predicted benefit from epidural injections of corticosteroid, without correcting for multiple statistical tests, it would be reasonable to criticize that conclusion. However, despite performing a large number of tests examining 21 predictors and 6 outcomes, we did not find any characteristics that consistently indicated better response to corticosteroid plus lidocaine than to lidocaine only. We concluded in our article that, "Our findings do not support the existence of a specific subgroup of patients with lumbar spinal stenosis that is particularly responsive to epidural injections of corticosteroid + lidocaine versus lidocaine alone." Regardless of any correction for multiple testing that could be performed, our conclusions would be unchanged. Thus, we do not think that either criticism listed in the two Table 4 footnotes is relevant to our study. [Footnote 1: unclear whether the subgroup variables were specified a priori; the hypothesized impact of subgroup on treatment effect was not stated. Footnote 2: large number of subgroups tested (i.e., subgroup hypothesis not one of a smaller number tested); was unclear whether any of the subgroup variables were specified a priori; the hypothesized impact of subgroup on treatment effect was not stated.] We note here that we did select all potential predictors</p>

generating hypotheses regarding these subgroups. Because GRADE evaluates the strength of evidence with respect to efficacy (albeit subgroup efficacy) and not with respect to hypotheses generating, studies considered to be hypothesis generating were downgraded for risk of bias so that such data isn't applied as efficacy results. Overall, your trial provided low risk of bias results with regards to the impact of ESI versus ENSI in spinal stenosis patients. However, the subgroup analyses performed were hypothesis-generating rather than hypothesis-testing, and thus the risk of bias was downgraded to address this limitation. Further, while we understand that a large number of potential subgroups were intentionally examined, doing so increases the chance of finding a significant interaction by change (i.e., a type-1 error) (Oxman and Guyatt) and thus increases the risk of bias surrounding the conclusions. Regarding the specification of subgroups a priori, we looked for clear statements that the subgroups were specified at the beginning of the study (rather than prior to conducting statistical analysis), as doing so protects against the potential for bias (see Oxman and Guyatt).

Note that this study was downgraded for risk of bias for the reasons described in footnote 2, not footnote 1.

Oxman AD, Guyatt GH. A consumer's guide to subgroup analyses. *Ann Intern Med.* 1992 Jan 1;116(1):78-84.

Comment		Response
	<p>examined prior to conducting any statistical tests, and as we wrote in our article, "All tests were considered exploratory and hypothesis generating. Therefore, we did not adjust for the number of statistical tests because we did not want to increase the risk of false-negative findings. However, we acknowledge that this increases the potential for false-positive findings."</p>	
<p>Executive Summary, Table 4</p>	<p>We point out that our study examined potential predictors of differential response to epidural injections of corticosteroid plus lidocaine versus lidocaine only. This study design does not address the question of which patients benefit from epidural injection of lidocaine plus corticosteroid versus placebo injections or other active treatment.</p>	<p>Thank you for your comment. This has been clarified in the Strength of Evidence table.</p>
<p>Public Comment: Steven R. Pollei, M.D., Medical Director, Center for Diagnostic Imaging, Federal Way and Lakewood, WA</p>		
<p>General</p>	<p>We appreciate the opportunity to comment upon the Spinal Injection Draft Evidence Report. In particular, we have concerns with the report's reliance upon data that fails to properly acknowledge the necessity of image guidance (fluoroscopy) in the delivery of epidural steroids. Indeed, the report suggests that fluoroscopy was utilized in only a handful (nine) of the 34 studies that were referenced in answering the many of the report's key questions. Further, it is unclear as to whether the studies that utilized fluoroscopy were separated from those that were conducted "blindly" in terms of efficacy or safety.</p> <p>Fluoroscopy allows physicians to confirm whether the location of medication delivery via needle was accurate, increasing both the efficacy of the procedure and patient safety. Further,</p>	<p>Thank you for your comment. The meta-analyses figures identify which trials used fluoroscopic guidance and which did not. All the trials using the transforaminal approach used fluoroscopic guidance, so for that approach, the argument is unfounded. Few trials of interlaminar and caudal approaches used imaging guidance which makes it difficult to determine the effect of fluoroscopy in those approaches. However, one can get some idea by looking at the Meta-analysis figures. For example, with respect to the efficacy of ESI for radiculopathy on pain improvement in the short-term (Fig.3), 1 of 3 trials used fluoroscopy with the caudal approach. Two of the trials not using fluoroscopy (Bush '91 and Datta '11) had the largest improvement in pain favoring ESI. These results don't support the argument that trials using fluoroscopy in delivering the epidural steroids using the causal approach would demonstrate better results than trials</p>

	Comment	Response
	<p>fluoroscopy can reveal anatomic derangements and abnormalities. Information regarding abnormalities is invaluable for determining the most efficient or the safest route for injection by the physician. Methods of "blind" injection, which this report appears to rely upon heavily, cannot confirm that the location of medication was accurate.</p> <p>One study regarding epidural steroid administration found only a 30% rate of success (epidural penetration) in patients when performing needle placement "blind" (White et al.), while another study reported a 97.5% rate of success when performing epidural steroid administration under fluoroscopic visualization (El-Khoury et al.).</p> <p>We would ask that the authors of the report re-consider its reliance upon studies that focused on techniques that are not the standard of care, much less in patients' best interest.</p>	<p>not using fluoroscopy. The situation is similar with respect to the interlaminar approach.</p>
<p>Public Comment: Brandon Messerli, D.O., EvergreenHealth, Kirkland, WA</p>		
<p>General</p>	<p>If one is interested in determining the effectiveness of a common and contemporary medical treatment, firstly a specific diagnosis must be chosen, secondly one identifies the current "gold standard" diagnostics to properly select subjects, and lastly a treatment is chosen specifically for that condition. In regards to the current practice of spinal injections, advanced imaging is nearly always necessary, and diagnostic blocks are mandatory in some cases, in securing a specific diagnosis. Only then can the optimal spinal injection treatment be administered. One example is that an acute foraminal disc herniation is approached by a transforaminal route for the epidural steroid injection. A caudal or</p>	<p>Thank you for your comment. We describe the patient populations and their diagnoses as they are reported in the studies. We report the results separately for different indications as reported by study authors. Diagnostic injections were not within the scope of this HTA. With respect to approach, we stratified results by injection approach in all the major analyses. There were no clear and consistent differences in efficacy when trials were stratified by approach. There was insufficient evidence to determine effects of imaging guidance because all trials of transforaminal injections used imaging guidance while only a few trials employing other approaches used fluoroscopic guidance.</p>

	Comment	Response
	<p>interlaminar injection will not reach the site of pathology, and fluoroscopic guidance is an absolute requirement to ensure the target was achieved. A second example is that lumbar facet pain cannot be diagnosed without dual, concordant medial branch blocks having provided substantial pain relief, and is a requirement before proceeding with medial branch radiofrequency neurotomy using 18 or 20G electrodes in specifically defined target zones for a defined ablation time.</p>	
<p>General</p>	<p>When performing a literature review regarding epidural steroid injections for lumbar radicular pain, it would be an error to include trials that lack methodological rigor. One would note that many older trials did not enroll subjects with imaging-confirmed pathology, and thus the injections were sometimes administered on subjects without the index condition. The heterogeneity of such studies precludes them from being helpful in answering the clinical question. One would also note that some trials did not choose an injection approach that ensures the injectate concentrates at the target, and some trials did not use imaging guidance at all. Data clearly shows that accuracy is unacceptably low if imaging guidance is not used. In either case, it is unknown if the injectate actually reached its target. Therefore, these studies are not helpful in answering the clinical question. Regarding outcomes data, one would note that results in this field are often bimodal rather than normally distributed; yet many studies only report continuous data rather than categorical data. The Ghahreman study (1) clearly demonstrated this fact; group mean data showed no benefit for ESI over the other study arms, but categorical data showed a significant and clear benefit. Of important</p>	<p>Thank you for your comment. With respect to outcomes that may be bimodal (i.e., some patients have a large clinically important response, and others do not), we report these data for pain, function and a composite outcome of both pain and function, to include the study to which the commenter refers (see Figs 6, 7, 8 for pain success; Figs 12, 13, 14 for function success; and Figs 15, 16 for a composite score success).</p> <p>There was insufficient evidence to determine effects of imaging guidance because all trials of transforaminal injections used imaging guidance while only a few trials employing other approaches used fluoroscopic guidance.</p> <p>Ghahreman 2010. The commenter has erroneously stated multiple times that this study was not included in our report. It is in fact included.</p>

	Comment	Response
	<p>note, this study and its categorical data was not included in Spectrum’s evidence report, despite it being perhaps the most relevant study for ESI.</p>	
<p>General</p>	<p>As a simile, imagine that the HTA reviews the effectiveness of azithromycin antibiotic treatment for community-acquired bacterial pneumonia. The key questions and evidence report allow for a review of RCTs assessing antibiotic treatment and cough. However, it failed to exclude trials that did not confirm the diagnosis with x-rays and cultures. Included studies thus included a heterogenous group of diagnoses, including viral and fungal pneumonia, hospital and nursing facility-acquired pneumonia, emphysema, asthma, heart failure, post-nasal drip, GERD, and cough due to ACE-inhibitor. Additionally, it failed to exclude studies that did not utilize the standard of care, such as azithromycin treatment for 5 days. Studies thus included a heterogenous group of inappropriate treatments, including 3 day antibiotic courses, IV antibiotics, and inappropriate use of penicillin in cases of penicillin-resistant bacteria or azithromycin for macrolid-resistant bacteria. It also failed to exclude studies that did not assess proper outcomes, such as resolution of cough or consolidation on x-ray at 3 and 6 weeks. The review also included studies that assessed continuous data. If half of subjects did not improve on antibiotics, because their cough was due to viral pneumonia or emphysema, then the mean data would show no significant benefit of antibiotic use.</p> <p>This hypothetical systematic review pooled data from studies with a heterogenous group of diagnoses, treatments, and outcome measures. The evidence vendor’s summary would state</p>	<p>Thank you for your comment. We describe the patient populations and their diagnoses as they are reported in the studies. We report the results separately for different indications as reported by study authors. Diagnostic injections were not within the scope of this HTA. With respect to approach, we stratified results by injection approach in all the major analyses. There were no clear and consistent differences in efficacy when trials were stratified by approach. There was insufficient evidence to determine effects of imaging guidance because all trials of transforaminal injections used imaging guidance while only a few trials employing other approaches used fluoroscopic guidance.</p>

	Comment	Response
	<p>that the quality of evidence is low, and that antibiotics are not efficacious for treatment of cough. Clearly this conclusion is erroneous. A more appropriate approach would have been to assess the 1 or 2 clinical studies with optimal methodology for proper diagnosis, treatments consistent with current practice guidelines, and appropriate outcome measures.</p>	
<p>General</p>	<p>It is unfortunate that the body of literature for spinal injections is not as consistently high-quality as one would hope. Fortunately, in the case of epidural steroid injections, there are several trials with methodology of very high quality, and these trials are certainly the best indicator of <i>current</i> clinical practice. These include the Ghahrman trial (1) that assessed categorical data, both Riew studies (2,3), and the Kennedy (4) and Kaufman (5) studies. The Kennedy (4) study is a prospective trial with optimal patient selection, injection technique, and outcomes data, and its results cannot be discounted simply because there was no placebo arm. An observational study by Kaufman (5) certainly has limitations due to its retrospective study design, but it must be considered since its methods utilized good patient selection, technique, and outcomes data, and it had a large sample size. The Ghahrman, Kennedy, and Kaufman studies were not included in Spectrum’s review, so further analysis should be completed before the March 18th HTCC meeting. MacVicar’s (6) systematic review of transforaminal ESI was not reviewed in Spectrum’s evidence report, but it should be reviewed by Spectrum as well, as it would be helpful in determining the methodological rigor of various studies.</p> <p>REFs:</p>	<p>Comments concerning the referenced publications are as follows:</p> <p>–Ghahreman 2010. The commenter has erroneously stated multiple times that this study was not included in our report. It is in fact included.</p> <p>–Riew 2000 and Riew 2006: Both studies are included.</p> <p>–Kennedy et al: This study was not included because it compared two different types of steroids for efficacy without a control injection (see inclusion/exclusion criteria)</p> <p>–Kaufman 2013: This was a retrospective observational study and as such did not meet the inclusion criteria.</p> <p>–MacVicar 2013: This was not a systematic review, but a narrative review without pre-stated inclusion/exclusion criteria. The authors included RCTs, comparative and non-comparative studies.</p> <p>–Tosteson 2008: This is a cost-effectiveness study comparing surgical to nonsurgical treatment for lumbar herniated intervertebral discs, and not a comparison of surgery to spinal injections.</p> <p>–Karppinen J: This cost-effectiveness study was included in the original report and remains in the current updated report.</p>

Comment	Response
	<p>–Ghahreman A, et al. The efficacy of transforaminal injection of steroids for the treatment of lumbar radicular pain. <i>Pain Med</i> 2010;11:1149–68.</p> <p>–Riew KD, Park JB, Cho YS, et al. Nerve root blocks in the treatment of lumbar radicular pain. A minimum five-year follow-up. <i>J Bone Joint Surg Am</i> 2006;88:1722-5.</p> <p>–Riew KD, Yin Y, Gilula L, et al. The effect of nerve-root injections on the need for operative treatment of lumbar radicular pain. A prospective, randomized, controlled, double-blind study. <i>J Bone Joint Surg Am</i> 2000;82-A:1589-93.</p> <p>–Kennedy DJ, et al. Comparative effectiveness of lumbar transforaminal epidural steroid injections with particulate versus nonparticulate corticosteroids for lumbar radicular pain due to intervertebral disc herniation: a prospective, randomized, double-blind trial. <i>Pain Med.</i> 2014 Apr;15(4):548-55.</p> <p>–Kaufman T, et al. Clinical Effectiveness of Single Lumbar Transforaminal Epidural Steroid Injections. <i>Pain Medicine</i> 2013; 14: 1126–1133.</p> <p>–MacVicar J, King W, Landers MH, Bogduk N. The effectiveness of lumbar transforaminal injection of steroids: a comprehensive review with systematic analysis of the published data. <i>Pain Med</i> 2013;14:14</p> <p>–Tosteson AN, Skinner JS, Tosteson TD, et al. The cost-effectiveness of surgical versus nonoperative treatment for lumbar disc herniation over two years: Evidence from the Spine Patient Outcomes Research Trial (SPORT). <i>Spine</i> 2008;33:2108–15.</p> <p>–Karppinen J. Cost-effectiveness of periradicular infiltration for sciatica. Subgroup analysis of a randomized controlled trial. <i>Spine</i> 2001;26:2587–95.</p>

	Comment	Response
	<p>In summary, a RCT with sound randomization, double blinding, and no losses to follow-up is of no value if the patients did not have the condition being studied and the procedure was not conducted accurately using contemporary techniques. As demonstrated by the example of antibiotic use for cough, stratification of studies by study methodology is of far greater importance.</p>	
<p>General</p>	<p>For further reference regarding these issues, I have attached 5 correspondences for the HTCCs review. The draft LCD could be used as a template for the HTCC when determining coverage decisions. The Rathmell article highlights the safety profile of non-particulate steroid use for epidural injections.</p> <ol style="list-style-type: none"> 1. The letter of September 15, 2015 from a multi-society pain workgroup to the HTA regarding the decision to re-review spinal injections. 2. The letter of December 15, 2014 from the International Spine Intervention Society to the AHRQ regarding the Draft Technology Assessment “Pain Management Injection Therapies for Low Back Pain”. 3. Baker R. “Demystifying Lumbar Transforaminal Epidural Steroids: A Seminal Efficacy Study of a Specific Spinal Injection”. Pain Medicine 2010; 11: 1141–1143. 4. Epidural Steroid Injections LCD Template from the Multi-Society Pain Workgroup. 5. Rathmell J. “Safeguards to Prevent Neurologic Complications after Epidural Steroid Injections Consensus Opinions from a Multidisciplinary Working Group and National Organizations”. Anesthesiology 2015; XXX:00-00. 	<p>In addition to the HTA, the HTCC will have access to the documents sent. Please note that Rathmell 2015 was summarized in the guideline section on page 57 and is reference #202.</p>

Comment	Response
<p>From an email sent separately (Multi-Society Pain Workgroup)</p> <p>To assist the HTA and Spectrum with considering further references for analysis, and finalizing the report by February 12th, I have listed in this email (including attachments) clinical trials, systematic reviews, policy statements, and associated articles that were not included in the draft report. Of note, the referenced systematic reviews came to different conclusions than Spectrum because they appropriately included non-RCTs and weighted the trials based on design. Also included below are web links for the Medicare/Noridian interventional pain LCD policies currently in effect in Washington State.</p> <p>I am hopeful that this tremendous body of work, culminating in Noridian’s LCD, will be of utility for the HTCC when determining coverage policies for the HCA. We trust that the HTCC will uphold the Washington Administrative Code 182-55-035, which states:</p> <p>(2) Identify whether the determination is consistent with the identified medicare decisions and expert guidelines.</p> <p>(3) For decisions that are inconsistent with either the identified medicare decisions or expert guidelines, specify the reason(s) for the decision and the evidentiary basis.</p> <p>Lumbar Transforaminal ESI <u>Clinical Trials:</u></p> <p>Kennedy DJ, et al. Comparative effectiveness of lumbar transforaminal epidural steroid injections with particulate versus nonparticulate corticosteroids for lumbar radicular pain due to intervertebral disc herniation: a</p>	<p>With respect to the literature cited, see comments below:</p> <p>Lumbar Transforaminal ESI <u>Clinical Trials</u></p> <p>Kennedy et al: This study was not included because it compared two different types of steroids for efficacy without a control injection (see inclusion/exclusion criteria)</p> <p>Kaufman 2013: This was a retrospective observational study.</p> <p>MacVicar 2013: This was not a systematic review, but a narrative review without pre-stated inclusion/exclusion criteria. The authors included RCTs, comparative and non-comparative studies.</p> <p>ESI Safety <u>Clinical Trial:</u></p> <p>El-Yahchouchi 2015: Published retrospective review of quality assurance databases and medical records. This study was published after our search dates.</p> <p>SI Joint <u>Clinical Trials:</u></p> <p>Liliang PC 2009: This is a case-series with no concurrent controls and therefore excluded from our report.</p> <p>Maugars Y 1996. This study assessed SI injections in patients with spondylarthropathy, a population not of interest for our review.</p> <p><u>Systematic Review:</u></p> <p>Kennedy 2015: This systematic review assessed the validity of fluoroscopically guided diagnostic intra-articular injections of local anesthetic and effectiveness of intra-articular steroid injections in treating sacroiliac joint (SIJ) pain. It includes two RCTs and several observational studies. It was</p>

Comment	Response
	<p>prospective, randomized, double-blind trial. Pain Med. 2014 Apr;15(4):548-55.</p> <p>Kaufman T, et al. Clinical Effectiveness of Single Lumbar Transforaminal Epidural Steroid Injections. Pain Medicine 2013; 14: 1126–1133.</p> <p><u>Systematic Review:</u></p> <p>MacVicar J, King W, Landers MH, Bogduk N. The effectiveness of lumbar transforaminal injection of steroids: a comprehensive review with systematic analysis of the published data. Pain Med 2013;14:14</p> <p>ESI Safety <u>Clinical Trial:</u></p> <p>El-Yahouchi CA, Plataras CT, et al. Adverse Event Rates Associated with Transforaminal and Interlaminar Epidural Steroid Injections: A Multi-Institutional Study. Pain Med. 2015 Nov 23.</p> <p>SI Joint <u>Clinical Trials:</u></p> <p>Liliang PC, Lu K, Weng HC, et al. The therapeutic efficacy of sacroiliac joint blocks with triamcinolone acetonide in the treatment of sacroiliac joint dysfunction without spondyloarthropathy. Spine 2009;34:896–900.</p> <p>Maugars Y, et al. Assessment of the efficacy of sacroiliac corticosteroid injections in spondylarthropathies: A doubleblind study. Br J Rheumatology 1996;35:767–70.</p> <p><u>Systematic Review:</u></p> <p>Kennedy DJ, Engel AJ, Kreiner DS, Nampiaparampil D, Duszynski B, MacVicar</p> <p>published after our search dates.</p> <p>Facet joint <u>Clinical Trials:</u></p> <p>Ackerman 2008: This study was not included because it compared two different types of steroid injections (intra-articular vs. medial branch nerve blocks) for efficacy without a non-steroid control injection (see inclusion/exclusion criteria).</p> <p>Dolan 1996: This study was not included because it compared two different scenarios (SPECT-positive vs. SPECT-negative) in which patients received steroid injections, without a control injection (see inclusion/exclusion criteria).</p> <p>Pneumaticos 2006: This study was not included because it compared three different scenarios (bone scintigraphy-positive vs. – negative, injection performed based on clinical referral only (no bone scintigraphy performed)) in which patients received steroid injections, but without a control injection (see inclusion/exclusion criteria).</p> <p>Policies</p> <p>We have added both the Noridian ESI and Facet Joint Local Coverage Determinations to Table 5 – Overview of payer technology assessments and policies for spinal injections – in the Background.</p> <p>Other Articles</p> <p>Rathmell JP 201: This publication is included in the report.</p> <p>Maus T. Submitted Fall 2014: These are comments directed to the AHRQ Report on spinal injections.</p> <p>Baker R. 2010: This is an editorial on spinal injections.</p>

Comment	Response
	<p>J. Fluoroscopically guided diagnostic and therapeutic sacroiliac joint injections: a systematic review. Pain Med 2015; 16: 1500-1518.</p> <p>Facet joint <u>Clinical Trials:</u></p> <p>Ackerman WE, Ahmad M. Pain relief with intraarticular or medial branch nerve blocks in patients with positive lumbar facet joint SPECT imaging: a 12-week outcome study. South Med J. 2008 Sep;101(9):931-4.</p> <p>Dolan AL, Ryan PJ. The value of SPECT scans in identifying back pain likely to benefit from facet joint injection. Br J Rheumatol. 1996 Dec;35(12):1269-73.</p> <p>Pneumaticos SG, Chatziioannou SN. Low back pain: prediction of short-term outcome of facet joint injection with bone scintigraphy. Radiology. 2006 Feb;238(2):693-8.</p> <p>Policies Noridian ESI LCD for Washington State: https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34980&ContrId=358&ver=2&ContrVer=1&CntrctrSelected=358*1&Cntrctr=358&name=Noridian+Health+care+Solutions%2c+LLC+(Noridian+Health+care+Solutions%2c+LLC+(02402%2c+A+and+B+MAC%2c+J+-+F))&LCntrctr=358*1&DocType=Active&bc=AAAAAIAAAAAA%3d%3d&</p> <p>Noridian Facet Joint LCD for Washington State: https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34995&ContrId=358&</p>

Comment	Response
	<p>ver=14&ContrVer=1&CntrctrSelected=358*1&Cntrctr=358&name=Noridian+Healthcare+Solutions%2c+LLC+(Noridian+Healthcare+Solutions%2c+LLC+(02402%2c+A+and+B+MAC%2c+J+-+F))&LCntrctr=358*1&DocType=Active&bc=AAAAAAIAAAAAA%3d%3d&</p> <p>Other Articles</p> <p>Rathmell JP, Benzon HT, et al. Safeguards to prevent neurologic complications after epidural steroid injections: consensus opinions from a multidisciplinary working group and national organizations. <i>Anesthesiology</i>. 2015 May;122(5):974-84.</p> <p>Maus T. AHRQ on the Draft Technology Assessment “Pain Management Injection Therapies for Low Back Pain” Comments Submitted Fall 2014.</p> <p>Baker R. Demystifying Lumbar Transforaminal Epidural Steroids: A Seminal Efficacy Study of a Specific Spinal Injection. <i>Pain Medicine</i> 2010; 11: 1141–1143.</p> <p>Multi-Society Pain Workgroup Recommendations on Interventional Pain Local Coverage Decisions.</p> <p>Department of Health and Human Services Office of Inspector General. LCD Determinations Create Inconsistency in Medicare Coverage. Jan 2014.</p>
<p>Public Comment: Belinda Duszynski, on behalf of a Multi-society (15) Review Committee</p>	
<p>General – Topic Selection</p>	<p>We question the decision to re-review the entire field of spinal injection based upon publication of one new study by Friedly <i>et al.</i> (1) and a U.S. Food and Drug Administration initiative to assess the risk of epidural steroid injections (2). In regards to the former, this clinical study</p> <p>This topic was identified for re-review based on publication of an FDA warning and a new RCT comparing epidural steroid injections to a non-steroid containing placebo in subjects with spinal stenosis. The updated review will include an updated literature search for the whole scope of the original review to ensure</p>

Comment	Response
	<p>the update review is current.</p> <p>Thank you for your comment. The focus of the safety section was placed on the evidence from randomized and non-randomized trials, which reported no catastrophic adverse events, very few major adverse events, and infrequent non-serious adverse events. The FAERS report was included for thoroughness in order to acknowledge that catastrophic adverse events have been reported, but that (as the FDA report concluded) such events are extremely rare and could not be causally linked to any particular injection site, route, injectate, or use of imaging.</p>
<p>did not pertain to the majority of spine pathologies, including: lumbar foraminal or lateral recess stenosis, lumbar disc herniations and radicular pain, facet or sacroiliac joint pain, or any cervical or thoracic pathology. Thus, there is no basis for a re-review of the efficacy concerning these conditions and their associated treatments, nor is there new evidence that would warrant a reversal of the coverage decisions made by the WA HCA Health Technology Clinical Committee (HTCC) in 2011.</p> <p>In regards to the FDA initiative, similar to nearly all medical treatments, there are known potential risks with epidural steroid injections. The most serious and lasting complications include spinal cord infarction or direct injury, brainstem and brain infarction, and spinal nerve root injury. The FDA’s concerns were raised on the basis of case reports – low quality evidence inappropriate for formulating practice recommendations. These reports were published prior to the 2011 WA HCA review of spinal injections, and were therefore considered in the 2011 WA HCA report’s safety discussion. In fact, the only new data available are from large studies showing safety of spinal injections. A recently published multi-institutional study examined more than 16,500 consecutive epidural injections performed in accordance with evidence-based guidelines in all spine segments with no major adverse events. (3)</p> <p>An expert working group with facilitation from the FDA’s Safe Use Initiative (SUI) and representatives from leading specialty societies reviewed the existing scientific evidence and assembled consensus clinical considerations aimed at reducing the risk of severe neurologic</p>	

	Comment	Response
	<p>complications. (4) The working group and the advising national organizations unanimously agreed that epidural injections of steroids were rarely associated with serious complications due to injuries of the central nervous system. They agreed that transforaminal injections are associated with a risk of catastrophic neurovascular complications and that particulate steroids appear to be inordinately represented in case reports of these complications. The representatives unanimously approved the clinical consideration that only non-particulate steroids should be used in therapeutic cervical transforaminal injections. Although use of non-particulate steroid dexamethasone as a first-line injectate in lumbar transforaminal injections was recommended, the representatives unanimously agreed that there might be instances where particulate steroids could be used in this setting (e.g., a patient fails to improve after an initial treatment with non-particulate steroid). Clinical considerations involving technical aspects of the procedures included the necessary use of appropriate image-guided views, injection of contrast under real-time fluoroscopy, review of prior imaging studies, use of facemask and sterile gloves, use of extension tubing, and avoidance of heavy sedation. Spinal injections should not be abandoned due to a very low risk of neurologic injury, particularly when appropriate measures can and should be utilized to substantially mitigate risks. Ultimately, the FDA has not modified the Black Box warning or limited use of corticosteroid for epidural steroid injections.(5)</p>	
<p>General – Report Develop-</p>	<p>Spectrum Research is a for-profit company that has been contracted to perform at least 14 separate health technology</p>	<p>Thank you for your comments. The legislation directs the Health Care Authority to contract for an evidence-based assessment with an</p>

	Comment	Response
<p>Methodology</p>	<p>assessments for the state of Washington. Given the established financial relationship between the two parties, and potential for reciprocity in the form of ongoing contracts which could be construed as a conflict of interest, at the very least the report itself should disclose this relationship between the two parties.</p> <p>The WA HCA website indicates that clinical experts may be consulted at various points throughout the HTA process. The clinical experts serving in any advisory role for the review must be intimately familiar with the intricacies of proper patient selection and study design, technical 'nuances' of proper injection techniques, and the utility of various outcome measures. The process for selecting these experts needs to be rational and transparent. Experts should be highly regarded among their peers in the field of interventional pain management. While the report indicates that a number of experts in various fields participated in this review, the lack of transparency about their names, expertise, and level of involvement is of concern. Involvement of individuals with subject-specific clinical expertise in the development of the report is critical.</p> <p>Washington State law RCW 70.14.110 states that the HTCC's decision cannot differ from Medicare or expert guidelines unless there is substantial evidence that their coverage decisions are wrong. Despite this requirement, the report failed to outline Medicare's coverage policies (e.g. Noridian's local coverage determinations on spinal injection procedures) or review expert guidelines published by the national medical societies vested in these treatments, such as those providing these comments. It</p>	<p>evidence-based practice center or similar entity. Spectrum meets these requirements and was identified and awarded through a competitive state contracting process.</p> <p>Three clinical experts were contacted and served in the advisory role. In addition, they each acted as peer-reviewers of the draft report. Their reviews and our responses to their reviews are part of this document. The clinical experts are listed in Appendix DDEC. They are:</p> <ol style="list-style-type: none"> 1. Pradeep Suri, M.D., M.Sc., Associate Professor, Department of Rehabilitation Medicine, University of Washington. 2. Daryl R. Fournery, M.D., F.R.C.S.C. (Neurosurgery), F.A.C.S., Professor, Division of Neurosurgery, Royal University Hospital; Saskatoon, Saskatchewan, Canada 3. James Babington, M.D., Medical Co-Director, Comprehensive Spine Program; Medical Director, Spine Clinics, Virginia Mason Medical Center; Seattle, Washington

Comment	Response
	<p>would be prudent for the HTCC to review these policies and guidelines, as they would provide assistance in determining coverage decisions, and it is necessary to ensure that state law is followed.</p> <p>Based on that state law, to restrict access to spinal injections, the burden of proof thus lies with the HTCC to prove these interventions are no better than placebo. Of the 142 conclusions reached, only two were based on high quality evidence, and these pertained to epidural steroid injections compared with epidural injections of local anesthetic in the treatment of one condition, lumbar central stenosis. (6) Only three conclusions were based on moderate quality evidence. There are 137 conclusions with low or insufficient evidence. When interpreting these conclusions, it is imperative that “low quality evidence” is not equated to “low treatment efficacy”.</p>
<p>General – Report Development Methodology: Absence of Peer Review Process</p>	<p>According to the report, “the information in this assessment is intended to assist health care decision makers, clinicians, patients and policy makers in making sound evidence-based decisions that may improve the quality and cost-effectiveness of health care services.” Peer-reviewed journals are meant to serve this purpose, as their editors are clinical and research experts who review manuscripts and approve publications only of the highest quality and ensure the absence of bias. It is of great concern that this technology assessment, which has bypassed the typical peer-review process by clinical experts, will be used to inform decisions that will potentially affect the care of millions of patients in the United States.</p>
<p>General – Evidence</p>	<p>Well-conducted RCTs remain the standard for evaluating the efficacy of an intervention.</p>

Comment	Response
<p>Base Restriction to Randomized Controlled Trials (RCTs)</p>	<p>clinical evidence, in making patient care decisions. (7) With a restriction to randomized controlled trials (RCTs) as the sole evidence to address questions of efficacy, the report ignores the best available evidence. The exclusion of high quality observational studies of clinical effectiveness removes important information and context from a synthesis of the literature. (7-9) In the recently published systematic review of long-term opioid therapy for chronic pain, Chou <i>et al.</i> highlighted the importance of observational studies in situations where RCTs fail to adequately assess effectiveness with consideration to important factors, such as type of pain and patient characteristics. (10,11) "Observational studies could also help address a number of these research questions, but should be specifically designed to evaluate patients with chronic pain prescribed long-term opioid therapy and appropriately measure and address potential confounders." (10)</p> <p>Recent methodology literature suggests that effect estimates from high quality observational trials do not differ significantly from RCTs. (9) Many of the RCTs that met the inclusion criteria established by the authors of this report include patients selected only by symptoms or in whom image guidance has not been utilized. These failings, further discussed below, make such trials irrelevant to current clinical practice and not unexpectedly show poor outcomes. Comparing non- image guided (blind) injections to injections performed in accordance with evidence-based guidelines (12) that achieve precise needle placement at a 1-2mm target zone in three- dimensional space with confirmation of medication distribution by</p>

Comment	Response
	<p>real-time observation of contrast flow has no validity. There are very few RCTs that utilize current practice standards. Hence, examination of recently published large observational studies adds important information that is more relevant to current standards of practice.</p> <p>There is no mandate by the WA HCA to limit technology assessments to RCTs. The choice to limit the review to RCTs was purposeful and inconsistent with prominent ideology regarding evidence-based medicine. (7) Evidence-based medicine involves identifying the best available evidence with which to answer clinical questions. An observational trial with appropriately selected patients and treatment indications, accurate and current treatment techniques, and appropriate outcome measures and time frames is far more relevant than an RCT with good randomization and blinding, but improper patient and treatment indications, antiquated or poor treatment technique, and weaker outcome measures.</p> <p>If all RCTs are analyzed as equals, simply because they have good randomization and low risk of bias, this does a great disservice to the scientific gains and practice improvements that the field of spine medicine has achieved in the last several decades. As an analogy, consider a hypothetical review of RCTs involving chemotherapy for breast cancer, spanning several decades of research, in which all of the studies were considered equivalent and pooled data were utilized. The efficacy of current diagnostic and treatment paradigms would appear erroneously poor, despite the clear gains this field has achieved in recent decades and years.</p>

	Comment	Response
	<p>Purposefully preventing a comprehensive and unrestricted evidence-based review is a great disservice to all stakeholders, as the review will come to erroneous conclusions, and the HTCC could egregiously deny access to procedures that truly can be beneficial. The ramifications of this cannot be understated. Patients could be left to suffer in pain; become dependent on risky and expensive medications; seek unnecessary, risky, and expensive surgeries; utilize additional health care resources; miss more work and incur time-loss payments and/or loss of taxable income; and other far-reaching consequences.</p>	
<p>General – Inadequate Subgroup Analyses for Each Question: Specific Diagnosis</p>	<p>We commend the authors of the report on making an attempt to define appropriate subgroups/diagnoses; however, the categories implemented (e.g. lumbar radiculopathy due to disc pathology and/or foraminal narrowing, lumbar radiculopathy attributed to multiple causes) represent a mixed bag of anatomic diagnoses, clinical syndromes without defined pathology, and inappropriate grouping of distinct diagnoses. The categories fail to adequately represent the way anatomic pathology and clinical presentation of symptoms are evaluated both clinically and in the literature.</p> <p>In the fields of interventional spine injections and surgery, it is imperative to secure an exact diagnosis before proceeding with a specific treatment. Clinical history-taking and physical examination alone have been proven to insufficiently elicit an exact diagnosis, and therefore the proper treatment remains unknown. Advancements in imaging provide substantial insight into anatomic</p>	<p>Thank you for your comment. We describe the patient populations and their diagnoses as they are reported in the studies. We segregated the data by indication given by the studies. There was insufficient evidence from study descriptions to determine with certainty the cause of symptoms, even when studies required confirmation by imaging. Please note that we present data separately for the following lumbosacral conditions: radiculopathy attributed to disc pathology and or foraminal narrowing, low back pain without radiculopathy, spinal stenosis, pain attributed to the sacroiliac joint, and pain attributed to the facet joint. Results from studies that have mixed conditions (i.e., radiculopathy due to HNP or spinal stenosis) are also presented separately.</p>

Comment	Response
	<p>pathology, and together with a history, examination, and sound medical judgment, will lead to a definitive diagnosis. Only then can a specific spinal intervention be offered and performed. Despite this necessity, several of the RCTs that met inclusion criteria for this report did not require advanced imaging to secure a diagnosis. Some of these trials are older studies that either did not have such advanced imaging at their disposal or were performed at a time when standard of care did not require imaging.</p> <p>It is critical to perform subgroup analyses by specific diagnoses. For example, there is no physiologic process beyond systemic effect by which steroids delivered to the epidural space would be expected to relieve axial back pain arising from nociception in the intervertebral discs, facet joints, sacroiliac joints, or supporting musculature. There is ample experimental and clinical evidence that radicular pain has an inflammatory basis and is potentially susceptible to targeted delivery of an anti-inflammatory agent to the interface of neural tissue and the compressive lesion. (13) For this reason, it is imperative that studies included in the assessment have diagnostic specificity, with correlative imaging findings as a requirement for inclusion.</p> <p>As an analogy, consider a hypothetical systematic review of prescription medication for the treatment of cough, a common symptom like low back pain. Studies may show beneficial effects from antibiotics in a group of patients with bacterial pneumonia, a specific diagnosis, whereas pooled data from heterogeneous groups of patients with cough – including viral bronchitis, chemical pneumonitis, asthma, lung cancer, <i>etc.</i> – would produce</p>

	Comment	Response
	<p>different effects. If these pooled effects showed that many different medications had minimal impact on cough from various sources, would we abandon prescription antibiotics for pneumonia?</p> <p>Additionally, the identification of the underlying etiologies of pain is essential as different pathologies not only have varying responses to treatment, but also have different natural histories, impacting prognosis. Thus, the time frame of follow-up to determine clinical utility becomes imperative. Some conditions, such as intervertebral disc herniation, can result in debilitating pain, but have an overall favorable natural history. This would be in contrast to neurogenic claudication due to central canal stenosis, which is less likely to resolve spontaneously with time. Thus short-term relief would be very appropriate and expected for pain caused by a disc herniation. To evaluate the long-term effects in this population would be as flawed as evaluating the long-term effectiveness of antibiotics for pneumonia. Again, should we withhold all antibiotics for pneumonia given the largely favorable natural history, or should we state antibiotics are ineffective because all subjects were better at 1 year follow-up? Similarly, should we withhold pain medications from patients with fractures or after orthopedic surgery, as these conditions only result in pain and have favorable natural histories?</p>	
<p>General – Inadequate Subgroup Analyses for Each Question: Imaging Guidance</p>	<p>The techniques utilized in the administration of epidural steroids are also critical. The authors of the report acknowledge that the use of image guidance was reported in only two of the studies of interlaminar epidural steroids for lumbar radiculopathy. However, they fail to separately analyze results based upon use of image guidance. Furthermore,</p>	<p>Thank you for your comment. The meta-analyses figures identify which trials used fluoroscopic guidance and which did not. All the trials using the transforaminal approach used fluoroscopic guidance, so for that approach, the argument is unfounded. Few trials of interlaminar and caudal approaches used imaging guidance which makes it difficult to determine the effect of fluoroscopy in</p>

	Comment	Response
	<p>while they state that image guidance is often used to improve accuracy of medication delivery, they do not acknowledge the impact of image guidance on outcomes. Data show that “epidural” injections performed without image guidance may not universally reach the epidural space, even in expert hands. (14-16) Off-target medication delivery may not be efficacious and may be dangerous. The report directly contradicts the FDA Safe Use Initiative on epidural steroid injections that demands image guidance. (4) To suggest to patients and physicians that epidural steroid injections do not require image guidance may create a significant potential for patient harm.</p>	<p>those approaches. However, one can get some idea by looking at the Meta-analysis figures. For example, with respect to the efficacy of ESI for radiculopathy on pain improvement in the short-term (Fig.3), 1 of 3 trials used fluoroscopy with the caudal approach. Two of the trials not using fluoroscopy (Bush 1991 and Datta 2011) had the largest improvement in pain favoring ESI. These results don’t support the argument that trials using fluoroscopy in delivering the epidural steroids using the causal approach would demonstrate better results than trials not using fluoroscopy. The situation is similar with respect to the interlaminar approach.</p>
<p>General – Inadequate Subgroup Analyses for Each Question: Approach, Access, Accuracy</p>	<p>While image guidance is essential, the technique of delivery is equally important. As with image guidance, the authors acknowledge that different approaches to the epidural space exist. While data are presented by different approach in the tables, the text and conclusions pool results from the various approaches together. Many midline interlaminar epidural steroid injection (ILESIs) and caudal injection studies suffer from the lack of image guidance; and even when performed with image guidance, these procedures may deliver medication distant from the site of pathology, without certainty that the steroid will reach, or in what concentration it will reach, the target zone in the ventral epidural space. In contrast, transforaminal epidural steroid injection (TFESI) procedures place the needle in direct proximity to the target nerve and verify delivery to that site by observing contrast media flow. (17) Recently described lateral parasagittal ILESIs have also been shown to preferentially deliver injectate to the target ventral epidural space. (18) It is not reasonable to combine these different</p>	<p>We stratified results by injection approach in all the major analyses. There were no clear and consistent differences in efficacy when trials were stratified by approach.</p>

	Comment	Response
	<p>injection techniques in an evaluation of “epidural steroid injections”. Many studies have shown that technically accurate injections will produce better outcomes. The only way to control for technical accuracy in a clinical trial is with blinded analysis of all procedure images and contrast media spread by independent reviewers. This has not been done in any of the studies included in the current report.</p>	
<p>General – Statistical Analysis: Inappropriate Weight to Continuous (Mean) Data</p>	<p>Many of the included RCTs report only continuous data as a comparison between group means in reference to a minimum clinically important difference. However, pain and functional disability treatment responses are rarely normally distributed. Rather, responses are often bimodal, with segregation into responder and non-responder populations. Group means will thus conceal a clinically significant response in the responders. Categorical outcomes that define the proportion of patients reaching a predefined responder status are critical to meaningful interpretation, as noted in the recent NIH Task Force recommendations on research standards for chronic low back pain. (19) Given the importance of relying on categorical data, acknowledged by the report’s authors, it is disappointing that the categorical data from the Ghahreman, <i>et al.</i> study were not included in the review. (20) When categorical data are available, they should be acknowledged and greater weight should be applied to these results than studies with mean data.</p>	<p>This is a repeat objection from a few commenters. However, it is unfounded in that we report categorical outcomes reaching a predefined level of improvement for pain, function and a composite outcome of both pain and function, to include the study to which the commenter refers (Ghahreman et al.) (see Figs 6, 7, 8 for pain success; Figs 12, 13, 14 for function success; and Figs 15, 16 for a composite score success). All such outcomes were included and evaluated separately from continuous outcomes in the summary of evidence tables.</p>
<p>General – Accuracy and Transparency of Data Presentation and</p>	<p>The stated aim of the report was to, “systematically review, critically appraise, analyze, and synthesize research evidence evaluating the efficacy, comparative efficacy, and safety of spinal injections in adults with subacute or chronic spinal pain.” Of the 142 conclusions reached,</p>	<p>See answers that correspond to the numbered comments below:</p> <ol style="list-style-type: none"> 1) The citation number for each trial included in the strength of evidence tables has been added. 2) The strength of evidence tables are summary tables. Specific outcome

Comment	Response
<p>Conclusions</p> <p>only five were rated “high quality”. This extensive document can only say very few things with any amount of certainty. One certain conclusion is that there is no difference between epidural steroid and epidural anesthetic in achieving short-term pain relief in the treatment of lumbar stenosis. It is unfortunate if this entire report was commissioned to make this one recommendation based on the “new literature” identified, namely the LESS trial by Friedly, <i>et al.</i> (1) Surprisingly, two of the other recommendations graded “moderate” or higher are in support of intra-articular facet steroid injections. This is despite a relative dearth of evidence in support of this procedure. This is in stark contrast to a number of high quality peer-reviewed systematic reviews on similar topics that have been able to arrive at significant conclusions. In the author’s literature search for such reviews, they failed to identify arguably the best reviews on epidural steroid injections for lumbar and cervical radicular pain by MacVicar, <i>et al.</i> and Engel, <i>et al.</i> respectively. (21-23) The tabulation of grading appears to give a semblance of transparency in the evaluation of a group of studies, but these data tables are far from transparent. Some examples of issues with the tables include the following:</p> <ol style="list-style-type: none"> 1) The individual papers comprising the sub-analysis for each subject in each table are not cited. Without appropriate referencing, it appears that RCTs may have been missing from the analyses in several tables. For transparency sake, it is critical to identify the studies. 2) A uniform definition of the various outcomes has not been provided across all tables. Successful outcomes 	<p>instruments used for pain and function are detailed for each study in the results tables, which are referred to in the results section of the text and found at the end of the document. Reproducing each detail in the summary strength of evidence table would defeat the purpose of this summary table.</p> <ol style="list-style-type: none"> 3) Each follow-up duration has its own analysis, and the commenter is referred to the results section of the report and the associated results tables. The strength of evidence summary table, again, is to provide an overall summary. When appropriate, we combined information. 4) See #3 above. The data are uniformly presented in the results section of the report and in the associated results tables found at the end of the document. 5) Thank you for catching this error. Sacroiliac joint pain was omitted from the strength of evidence tables by mistake; the mistake has been corrected. 6) Regarding catastrophic adverse events, none were reported in the included randomized trials or cohort studies, thus we did not differentiate between lumbar and cervical injections. The report of the FDA Adverse Events Reporting Database made no conclusions regarding the risk of catastrophic adverse events following lumbar versus cervical injections; catastrophic events were reported following injections at both sites. As such, we chose not to generate conclusions for lumbar versus cervical injections. The conclusions regarding serious adverse events were that they were rare across all included studies, and the only reported events were stratified by injection site in the SoE table. Finally, the conclusions regarding non-serious adverse events

Comment	Response
<p>should be clearly defined for all categories in all tables.</p> <p>3) There are inconsistent analyses across categories by duration of follow-up (e.g. combining intermediate and long-term in some categories and not others).</p> <p>4) There is not uniformity in the tables for reporting all outcomes data at each time point. It appears the authors have arbitrarily selected outcomes and time points as was seen fit, rather than uniformly listing studies in all categories.</p> <p>5) If evaluating facetogenic pain, the data presentation should be comprehensive. ▪ It is unclear why sacroiliac pain is omitted from Table 1.</p> <p>6) There is obviously a risk differential between cervical and lumbar interventions, the types of interventions, and the injectates utilized. The grading of studies in Table 3 does not take this into account, but lumps them altogether.</p> <p>7) Transparency is required in delineating how the authors have reached the conclusions. “ESI for disc and foraminal compression” simply states “no significant difference” and “low quality evidence”. Without additional explanation, the assessment appears arbitrary.</p> <p>Meaningful conclusions cannot be derived without re-analyzing the data after excluding all RCTs in which no confirmatory imaging was done or reported, no fluoroscopic guidance was used (most old studies), and no caudal epidural steroid injections were allowed. This analysis should also stratify results of each treatment by diagnosis [e.g. TFESI for acute/subacute pain, TFESI for acute</p>	<p>were that the majority occurred infrequently but were generally not well-reported. As the same conclusion held for both lumbar and cervical injections, we chose not to stratify the conclusions.</p> <p>7) For the example given regarding ESI for radiculopathy due to disc and/or foraminal narrowing, the table provides the effect estimate (weight mean difference (WMD), standardized mean difference (SMD), risk ratio (RR)) for all pooled analyses. The conclusions we draw are directly related to whether the estimates indicate a treatment effect. In the majority of cases they did not show any difference between groups for a given outcome. The purpose of the review is to summarize the evidence, not to make clinical or policy recommendations. Regarding the quality rating, the detailed version of the strength of evidence tables, which provided information regarding why the evidence was up- or downgraded base on the various domains assessed (risk of bias, inconsistency, indirectness, imprecision), are now included in the Executive Summary.</p>

	Comment	Response
	single-level HNP, TFESI for low-to-moderate grade compression, <i>etc.</i>].	
General – General Public Health Concerns	<p>A systematic review of a specific topic is not required to take into consideration a plethora of other factors that are prudent when a physician and patient decide to pursue a treatment. On the other hand, a committee making coverage decisions does need to consider the bigger picture. Some patients may have no other options apart from spinal injections. Implicit in this discussion of spinal injections is that conservative care (e.g. physical therapy, chiropractic, medications, <i>etc.</i>) has failed. Surgery can be contraindicated due to comorbidities or age, and some patients are adamant that they want to avoid surgery at all costs. Surgery also entails the very real risks of immediate or delayed surgical failure, technical failure, serious infections, permanent paralysis, re-herniations, and subsequent segmental instability requiring fusion. Several authors reported significantly worse outcome of discectomy in those with small, contained disc herniation. (24-26) Some even excluded from surgical consideration patients with small size lumbar disc herniation. (27) Thus, for patients with radicular pain because of a small disc herniation, surgery is far from a guaranteed solution. These are relevant considerations in the broader scope of clinical decision-making between a patient and physician.</p> <p>Chronic or palliative care is also not always a good option. Opioids and NSAIDs can be contraindicated due to comorbidities, and both may have only short-term and minimal benefits. A large, utilization review, conducted in Denmark, of 2,000 patients who used opioids long-term for chronic pain, found that opioid therapy failed to fulfill any of the</p>	Noted. The purpose of the review is to summarize the evidence, not to make clinical or policy recommendations.

Comment	Response
	<p>treatment goals: pain relief, improved quality of life, or improved functional capacity. (28) Long-term opioid therapy has very real and serious adverse effects, such as physical dependence, tolerance, opioid-induced pain hyperalgesia, addiction, diversion, and abuse; and side effects such as impairment of the immune, endocrine, and reproductive systems. (29-32) Increasing abuse and diversion of prescription opioids have become a serious problem. According to the Centers for Disease Control and Prevention (CDC), during 2014, 28,647 (61%) drug overdose deaths involved some type of opioid, including heroin. Prescription opioids killed 19,000. (33)</p> <p>Regarding NSAIDs, a study in the <i>New England Journal of Medicine</i> estimated that at least 103,000 patients are hospitalized per year in the United States for serious gastrointestinal complications due to NSAID use. (34) At an estimated cost of \$15,000 to \$20,000 per hospitalization, the annual direct costs of such complications exceed \$2 billion. This study also estimated that 16,500 NSAID-related deaths occur every year in the United States. This figure is similar to the annual number of deaths from AIDS and considerably greater than the number of deaths from asthma, cervical cancer or Hodgkin's disease. NSAIDs can be considered to be the 15th most common cause of death in the US.</p> <p>There is no doubt that spinal injections are not the panacea for all spinal conditions. There are conditions best treated conservatively and others best treated surgically. Spinal injections provide a valuable alternative option for some people. And unlike some medical treatments, which “cure” a problem (e.g.</p>

	Comment	Response
	<p>appendectomy), many spinal conditions cannot be cured. Repetitive, palliative treatments can be the only option. The risk-benefit ratio of repeated spinal injections can sometimes be preferable to perpetual medication use, or simply living with pain and disability.</p>	
<p>Summary</p>	<p>It is imperative to recognize that study methodology is meaningless unless the procedures being assessed are performed on appropriately selected patients with appropriate indications using accurate and current technique. An RCT with sound randomization, excellent blinding, and no losses to follow-up is of no value if the patients did not have the condition under investigation and/or the therapeutic procedure was not conducted accurately. Stratification of studies by appropriate patient selection and acceptable, technical performance of the procedures is critically important and must be considered in parallel with, or even precede, evaluation of study design in assigning value to a study. Because the methodological limitations outlined above, the current draft of the report does not adequately address the key questions posed and is not a satisfactory reference for the topic.</p>	<p>This review summarizes the highest quality peer-reviewed literature on efficacy and safety. Given that well-conducted randomized trials are the standard for efficacy of interventions and that there were nearly 50 trials of injections available for review, we feel confident that these studies adequately address the key questions. We believe that observational studies can be useful for harms and in certain instances, effectiveness. However, they are highly susceptible to confounding and bias, and have been shown to be misleading when evaluating the effectiveness of interventions based on subjective outcomes such as pain. We do not believe that observational studies should take precedence over higher-quality randomized trials. And given that nearly 50 trials of injections exist, we do not believe that trials are lacking in this area.</p>

APPENDIX: REVIEWS AND COMMENTS RECEIVED**PEER REVIEW****Comprehensive Evidence-Based Health Technology Assessment Peer Review Form**

Thank you for your willingness to read and comment on the Comprehensive Evidence-Based Health Technology Assessment Review for the **Spinal Injections Re-review Report**. Your contribution and time are greatly appreciated. The general time commitment ranges between 2 and 4 hours; we are able to pay a maximum of 6 hours.

This form can be filled out electronically on your personal computer. Enter your identification information and comments directly into the shaded areas; use the **TAB** key to move from field to field. Please enter the section, page, and line numbers where relevant. The shaded comment field will expand as you type, allowing for unlimited text. You have been provided comment fields in each section. Should you have more comments than this allows for, please continue with a blank page. Additionally, we are very interested in your evaluation of the ease of use of our Peer Review Form. Please use the last field to enter suggestions for improvement.

We will be going through the draft for typographical errors as well as grammatical and minor edits, allowing you to focus on the substance/content of the report.

When the Peer Review form is complete, save it to your hard drive and return as an e-mail attachment to: joe@specri.com

PEER REVIEWER #1: James R. Babington, M.D.

Reviewer Identification Information

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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 2 Line Policy context

While the FDA did place warning labels on the use of epidural corticosteroid injections, this did not constitute a significant change from the known risks. The outcome of the working group convened by the US FDA Safe Use Initiative did make specific recommendations to mitigate the risk of rare, but well-recognized complications of epidural steroid injections (Benzon et al *JAMA*. 2015;313(17):1713-1714). Adherence to best practices can help improve the safety profile of any procedure, but is unlikely to “eradicate” it. Imaging guidance is recommended for all cervical spinal injections.

Page 3 Line population

Patients with subacute and chronic pain are part of the review. Is there a specific reason why patients with acute pain < 4 weeks duration are excluded?

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?

Background accurately describes the scope of the problem. Unfortunately, the text suggests that spinal injections have a role in the treatment non-specific spine pain. It does not address the appropriate use of spinal injections. While non-specific low back pain does not have a high correlation with imaging findings as described in van Tulder et al (*Spine* 1997; 22: 427-434), this is not the patient population where injections should be employed. Appropriate use of injections, focuses on the treatment of

patients with a history and physical exam that is supported by imaging findings. The inclusion of coverage policies from other carriers is helpful as are guidelines.

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 32 **1**

Spinal injection procedures are not indicated for non-specific low back or neck pain. The disease and treatment paragraphs suggest that the use of spinal injections may be applied in that patient population. Spinal injections are a targeted treatment for specific spinal conditions within the context of a patient history and physical examination that is supported with concordant anatomic abnormalities on imaging studies. Spinal injections should be considered directed procedures aimed at treating a defined pathoanatomic etiology for pain.

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?

Page 78 **Line**
Interventio
n

Although the analysis stratifies based on condition, there are instances where the condition is poorly defined in the primary paper. The etiology for the symptoms is key in fully understanding the response to any treatment. Combining multiple etiologies for the painful condition will lead to erroneous conclusions. Additionally, myriad technical approaches are employed and combined in the analysis for efficacy. For example, image guidance is used in some studies and not in others. Caudal, interlaminar, and transforaminal techniques are all combined in the analysis yet most practicing interventional spine would agree that there are vast differences between each. This is misleading in developing a determination for efficacy.

Page 79 **Line Study**
design

The use of only RCT to determine the efficacy under KQ1 limits a comprehensive understanding of the literature. Medical science routinely uses RCTs to determine efficacy however there is a rich level of experience and knowledge that is obtained using other types of studies. To exclude them is limiting significant information that is routinely used to provide care to our patients. The observation of

outcome particularly in an interventional/surgical area where randomization cannot easily be performed should not be discounted. Evidence based practice is the integration of best research evidence, clinical expertise, and patient's values (Sackett DL, et al. BMJ 1996; 312:71-2). To be good stewards of our practice we need to ensure that inflexible rules do not produce care that is management driven and not patient centered (Greenhalgh T et al. BMJ 2014; 348: g3725).

Page 80 **3.1.3**

Regarding literature search. It would be helpful to know which "reference lists of relevant studies" and "several systematic reviews" were used.

Stage three a priori inclusion criteria are not explicated.

Page 82 **3.1.5**

The determination of strength of evidence initially seems straight forward and to be based on the fact that the evidence results from a randomized controlled trial. However, it appears that the SoE can be up or downgraded based on a qualitative assessment of risk of bias, consistency, directness, precision, and publication bias. It is not entirely clear how those factors are objectively applied and weighted to influence the strength of evidence that is ultimately reported.

Page 83 **3.1.6**

It is challenging to accept that the Weighted Mean Difference is an accurate estimate of outcome for pain when the interventions are significantly different in approach and medication delivered.

Regarding, missing standard deviations were other methods for imputing missing data sought and did they yield a different result from using other studies to estimate the values?

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 sufficient though it is an enormous challenge to address the entire field of spinal injections in a single report. The key questions are addressed though the conclusions do not reflect the current state of practice. There are no recommendations to address limitations in the literature rather conclusions are drawn based off of low quality primary studies.

Page 86 **Line 4.1.2**

34 RCTs are assessed. The etiology includes foraminal stenosis and disc degeneration which are combined in assessment. Treatment included non-image guided, ultrasound guided, and fluoroscopically guided injections. Approaches spanned caudal, interlaminar and transforaminal techniques. Injectates included five different medications. This analysis does not reflect current practice standards and does not give appropriate data to draw relevant conclusions regarding efficacy.

Page 92 **4.1.4**

Trials included a variety of etiologies for spinal stenosis. Only three studies required confirmation by MRI or CT scan for the presence of spinal stenosis. Again myriad treatments and techniques hamper the ability to make sound conclusions.

Page 94 ESI vs disc procedures

The MILD procedure is not a disc procedure. This procedure addresses hypertrophic ligamentum flavum via a percutaneous approach.

Page 100 4.1.8

Epidural steroid injections are not indicated for the treatment of sacroiliac joint pain. It should read “sacroiliac joint injections” rather than “epidural steroid injections”.

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 results of this analysis are not sufficient to detect differences between groups. The major challenges are absence of quality basic clinical evidence for these procedures using current techniques, neglect of other sources of information, and the heterogeneous nature of diagnosis and treatment approaches. The more accurate assessment is that there is insufficient high quality RCT data to reach a definitive conclusion.

The only conclusion based on presumed high quality data was in the injections for the treatment of lumbar stenosis. Interestingly, although there is no difference in “pain success” or “function success” there was statistically significant improvement in both the treatment and control arms of the trial cited here. This suggests that patients did improve with spinal injection into the epidural space however there was no significant difference in pain or function between the steroid and local anesthetic group.

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 report is well structured and organized. Main points are clearly presented. The focus and use of only RCTs belies current practice. The report emphasizes the rapid increase and overuse of spinal injections while suggesting there is little good evidence for injections in the treatment of spine pain. The assessment of appropriate use of spinal injections is important for public policy, however the conclusions drawn erroneously suggest that spinal injections are not relevant in this treatment arena. Other well performed studies have come to vastly different conclusions than this report. Clinical experience in well-selected patients suggests that this is a treatment approach that provides significant benefit to patients who have few other therapeutic options and may be reasonable when used appropriately.

QUALITY OF REPORT

Quality Of the Report

(Click in the gray box to make your selection)

Superior

Good

Fair X

Poor

We would appreciate any feedback you have on the usability of this form. Please add comments in the field below.

It would be helpful to have line numbers throughout the document.

It would be helpful if the titles in the survey matched exactly the titles used in the draft document.

PEER REVIEWER #2: Daryl Fourney, M.D.

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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 1-2 Line

The introduction provides a overview of the topic and highlights the increasing use (and therefore cost) of spinal injections to treat neck and back related pain, especially when there are significant concerns about the efficacy and safety of these procedures

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 45-76 Line

The content of background information is sufficient. The background raises the points about new safety concerns from the FDA, and new literature that addresses safety and (particularly long term) effectiveness. Here is an overview of the types of procedures, the mechanism of action. Published guidelines are reviewed as well as previous systematic reviews. Finally, there is an overview of Medicare and private insurance coverage policies.

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 33 **Line**

Objective was to update previous review. The key questions address all relevant questions regarding safety and effectiveness, including analysis of patient sub-populations which may or may not benefit from the intervention, the type of intervention and the provider. As well direct and comparative costs are questioned

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?

Page 78-84 **Line**

The inclusion/exclusion criteria for studies is succinctly outlined in Table 6. New publications were searched from 2010-2015 to supplement the previous review. After exclusions, there were 120 new articles included. The strength of evidence for studies was assessed using standards as outlined on page 82. The method used is consistent with the latest principles in evidence-based medicine and has been accepted in multiple peer-reviewed systematic reviews by the authors. Strength of evidence for economic studies is problematic, as outlined by the authors on page 82, because standardized methods for determining the strength of evidence for these studies is not generally accepted. This affects key question 4. Overall, the data abstraction method was very rigorous and standardized.

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?

Page 85-147 **Line**

There is a tremendous amount of detail provided, but the authors have done a great job summarizing it in table form. A large number of tables is required given the multitude of comparisons for different techniques and length of follow-up. The strength of evidence is listed for each outcome assessed. The authors have presented the conclusions in an unbiased manner. There is very little published in term of cost effectiveness data, and the authors have summarized this well (page 147).

CONCLUSIONS Comments

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

- Are the conclusions reached valid?

Page	Line
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The conclusions stated for individual studies appears fair and unbiased. There are no overall conclusions for policy based on the results of the review.

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?

Page	Line
------	------

This is a very detailed, well written review encompassing all relevant clinical and cost-related factors pertaining to therapeutic spinal injections. Points are presented in a clear unbiased fashion. Due to multiple comparison studies using different techniques and follow-up time, there are a large number of tables, but a certain level of granularity is required so that different studies are not lumped together inappropriately. I think that the authors have achieved a good balance here. This type of critical analysis is very important for public policy given the growing burden of chronic pain in society and the associated costs of treatments which may or may not be appropriate.

QUALITY OF REPORT**Quality Of the Report**

(Click in the gray box to make your selection)

Superior X

Good

Fair

Poor

PEER REVIEWER #3: Pradeep Suri, M.D., M.S.

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REVIEWER NOTE: No line numbers were provided on the review document, and therefore all comments below list only page numbers.

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 generally very thorough and certainly adequate. The topic of the assessment is important, and the clinical and policy relevance are well defined.

Page 1 **Line**

“In general, spinal injections are indicated for average pain levels greater than 6 on scale of 0–10; intermittent or continuous pain causing functional disability; or chronic pain that has failed to respond to more conservative therapies.”

- There is no universally accepted cutoff for what level of pain on a NRS or VAS is sufficient to warrant spine injections. I would recommend this cut-off off 7/10 be removed, or stated as specific to the sources cited with qualification that there is no widely accepted cutoff. This cutoff for pain is also mentioned on page 49- “In general, epidural, facet joint, and sacroiliac joint injections are indicated for average pain levels greater than 6 on scale of 0–10”.

Page 44 **Line**

2nd paragraph from bottom of page- the word ‘face’ is written instead of ‘facet’

Page 50 **Line**

“2.2.5. Particulate and Non-Particulate Steroids:”:

In this section it might also be mentioned that there is an opinion among many clinicians that particulate steroids have greater positive effects than non-particulate steroids (although not

necessarily with clear evidence supporting this view). It is also held that the issue of particulate vs. non-particulate steroids (and the greater risk of particulate steroids for catastrophic AEs) is greater with transforaminal epidurals, and is either not present or is much lower with interlaminar epidurals.

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 literature review and background is sufficient, and clearly written.

Page 45 Line

I would recommend using alternate terminology to replace the dated term ‘degenerative disc disease’, which has been out of favor for some time due to the near-ubiquitous nature of disc degeneration in middle to older age adults. The terminology ‘disease’ alone can be damaging for patients to hear, and can reinforce illness conviction and maladaptive pain beliefs. I would recommend if possible to use the less polarized term ‘disc degeneration’ as a substitute and to list ‘disc degeneration’ as a synonym if needed, or at a minimum to acknowledge the limitations of the term ‘degenerative disc disease’.

Page 47 Line

The epidural procedure descriptions on this page underlie the conceptual rationale for why the results of RCTs pertaining to these fundamentally different procedures (ESI IL vs TF vs. caudal) should not be pooled together in a meta-analysis. See further comments on this below

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?

The aims and questions clearly address relevant policy and clinical issues, although some, such as key question 3, seem well beyond the current state of the scientific literature. The 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?

The method for identifying relevant studies is rigorous in terms of the literature search, evaluation of study quality, study characteristics, and study risk of bias. The reviewers should provide an explanation for why acute radicular pain <4 weeks was a study exclusion criteria, since ESIs are sometimes done for intractable acute radicular pain, especially when pain is very severe and the only other option is surgery.

The methods for LOE are appropriate and clearly explained.

The data abstraction and analysis review are generally adequate. However, various important clinical criteria were not accounted for in terms of classifying studies. In particular, various different types of interventions were pooled together in a manner that I believe to be inappropriate based on clinical/conceptual reasons.

The review in various locations comments on differences with respect to injection approaches for ESI (such as TF vs. IL vs. caudal, pp 47-51), the separation of fluoroscopic vs. non-fluoro guided procedures, and control groups (e.g. ENSI vs. NEI), which highlights very important conceptual and technical distinctions between these procedures. However, these distinctions were largely ignored in the results summary/meta-analysis, and groups were simply pooled with respect to these various subgroups.

Regarding injection approach: the 3 major ESI procedures in the review (TF vs. IL vs. caudal) are quite different from one another technically, as is described in the document, and in my opinion there is no compelling conceptual reason why one should pool the results of these different procedures. They are different procedures. The risk factor profiles for the different ESI approaches are also conceptually different, based on anatomic considerations. For instance, TF ESIs (with particulate steroid) are most commonly the procedure type implicated in the rare occurrence of catastrophic ESI-related AEs resulting in paralysis, with substantially lower risks for these types of catastrophic AEs in IL or caudal ESIs. These conceptual reasons underscore why the results should be presented separately via approach, and not pooled in the texts, figures and/or tables. Regarding fluoroscopic guidance: the lack of fluoro guidance for a specific trial means that such a trial did not and could not confirm that steroid was actually placed in the epidural space. All of these trials without fluoro guidance could therefore result in some misclassification of the intervention itself (is actually steroid placed in the epidural space?), and bias towards a null result for those trials. The necessity for fluoro guidance is underscored by the 2015 US FDA guidelines to prevent neurologic complications that is described on pp. 57-58 ("Safeguards to Prevent Neurologic Complications after Epidural Steroid Injections (2015)"). Regarding the classification of control groups (ENSI vs. NEI): these different types of controls are pooled together in many of the figure/table analyses. Some of the controls included in these RCTs are believed to be 'active controls' with various levels of short term effects. The putative effects with these controls are generally stronger for epidural injections than non-epidural injections (the ENSI vs. NEI distinction), and there are robust short-term benefits with steroid even if placed outside the epidural space (a steroid vs. no steroid distinction, irrespective of epidural vs. non-epidural placement). The Bicket review (8) cited in the paper refers to some of these issues, and calculates an indirect comparison of ENSI vs. NEI that is suggestive of real differences (albeit such differences were not seen in the 2 studies illustrating direct comparisons).

Another important issue is the time frame of follow-up used in the review. The shortest-term follow-up duration included in the review is ≤ 3 months. This obscures our understanding of what happens in the very short term (≤ 1 month) after these procedures. This is particularly important since the duration of effect for these procedures is often very short (often ≤ 1 month), and the treatment effect would be expected to have mostly disappeared by 3 months. Not registering what happens in the very short term is part of what creates this chasm between what clinicians/patients observe in the immediate/very

short-term, and what clinical studies pick up when the first follow-up assessment is at a 3-12 month time frames. I would recommend a separation out of immediate/very short-term results (≤ 1 month) from short-term results (2-3 months).

A distinction not commented on is the combining of anesthetic control injections and saline/water (without anesthetic) control injections into one control group. For TF epidural injections of anesthetic, and also for IL epidural injections of anesthetic to a lesser degree, patients with lumbosacral (LS) radicular pain will often be able to discern when they have an epidural with anesthetic, because an anesthetic-only epidural will temporarily block radicular pain corresponding with a specific nerve root, depending on the placement of the injection. For instance, a TF epidural injection of anesthetic (without steroid) is very similar to a 'selective nerve root block' (SNRB). In an SNRB, the disappearance or relief of typical radicular pain indicates the specific nerve root level of pain. This would have differential effects on blinding with a TF epidural with anesthetic, as compared to a TF epidural performed with saline. This argues against pooling the results of studies using these two types of control injections, at least with respect to very short-term outcomes. In addition, there are many clinicians who believe that anesthetic injections into the epidural space- and elsewhere- can have therapeutic benefits beyond the usual expected duration of anesthetic effects, and beyond that seen with epidural saline, albeit very short term.

My comments as above pertain to the 'Efficacy Results' and Table 1 beginning on page 5, and also pertain to figures 3-22 and their corresponding tables. Of note, statistical explanations for why pooling is or is not justified are irrelevant due to the conceptual reasons stated. To my knowledge, statistical methods such as heterogeneity testing, subgroup interactions, and the profile likelihood method cannot address the conceptual problems with pooling distinct procedural categories. I'd recommend that the results be presented separately by approach, with or without fluoro guidance, etc.

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?

In general, the level of detail was excellent with the extensive results section. It is clear that meticulous attention has been paid to many aspects of the lit search, data collection, and extraction. Further comments below

I can't find clear statements regarding answers regarding 2 aspects of the 4 key questions. For instance, I wasn't able to find the conclusions regarding efficacy related to repeated spinal injections, multilevel spinal injections, and bilateral vs. unilateral spinal injections (key question 1). I also can't find any

statement regarding conclusions pertaining to treatment modifiers by steroid particulate size (key question 3, page 77).

Page 92 **Line**

“Patients were included if they had chronic function-limiting back and/or leg pain or signs of neurogenic claudication; MRI or CT confirmation of spinal stenosis was required in three studies.”

- If only 3 studies had MRI or CT confirmation of spinal stenosis, the other studies are not actually studies of interventions for symptomatic lumbar spinal stenosis or lumbar spinal stenosis (it cannot be known if patients have actual lumbar spinal stenosis without MRI/CT/CT myelogram or myelogram). They may be studies of claudication or claudicatory-type pain, but cross-sectional imaging is a sine qua non for diagnosis for lumbar spinal stenosis or symptomatic lumbar spinal stenosis.

-

“Due to the large amount of heterogeneity ($I^2=55\%$), we excluded one outlier trial (mean difference - 0.81 compared with all others ranging from -0.20, 0.30). Excluding the outlier trial decreased statistical heterogeneity, ($I^2=0\%$), reduced the overall point estimate, mean difference 0.08 (95% CI: -0.12, 0.28) but did not change the overall results.”

-In Figure 18, the total heterogeneity appears to be listed as $I^2=74\%$, not 55%. If this exclusion of outliers was done based on heterogeneity, it is unclear why similar checks for the reasons underlying high total heterogeneity were not done for other of the metaanalyses/figures featured, given high I^2 s such as Figure 3 ($I^2=97\%$), Figure 4 (98%), Figure 5 (90%), and other figures up to Figure 21.

Page 87, 92 **Line**

P87- many of the trials included of IL (8/10) and caudal ESI (5/6) for lumbar radiculopathy did not include fluoroscopic guidance. As mentioned above, this means that those trials did not and could not confirm that steroid was placed in the epidural space. All of these trials could result in some misclassification of the intervention itself, and bias towards a null finding.

P92- 4/10 of the ‘LSS’ trials did not use fluoroscopic guidance, and for 2/10 the use of fluoro was unclear. These trials did not and could not confirm that steroid was placed in the epidural space.

Page Tables **Line**

Table 1 and Table 2- for the final version of these tables, it would be extremely helpful to cite the publications (citation numbers) in the actual table so they can be more easily looked up. In the current form, it is impossible to quickly check the details of what is in the table without spending hours going back and forth to various parts of the document.

Table 1, page 7: for the study cited as “No difference between ESI and posterior ligament injection of saline + oral gabapentin in pain or function, or the likelihood of achieving pain success”: I believe this is referring to the BMJ 2015 Cohen trial of ESI vs. gabapentin. This should mention that the ESI intervention also involved oral placebo pills as part of the intervention.

For those interventions including ‘extra-articular’ injections, it would be good to clarify where in the extraspinal structures these injections were placed, even if as a table footnote.

Table 2 p 17: One of the rows under “Facet pain: IASI versus Intra-articular control injection” lists “More improvement in pain with ESI versus ENSI.” I believe this was meant to state ‘more improvement with intrarticular steroid than with intraarticular nonsteroid

Table 3- Due to the conceptual distinction of AE risk according to the ESI approaches (TF vs. IL vs. caudal), it would be useful to have the Table 3 FDA AE reporting database events stratified by injection approach. This is most pertinent because the catastrophic AEs related to particulate steroid use are believed to be most pertinent to transforaminal ESIs, and more rarely a consideration in IL and caudal ESIs (although to my knowledge all ESI types have had case reports of catastrophic AEs).

Regarding the cost-effectiveness results: these are very clearly described, however the description of Arden/Price 2006 should likely state explicitly in the Executive Summary and Results sections that the trial did not use fluoroscopic guidance, which might have efficacy and cost implications.

Page 84 **Line**

Page 84 reads “We assessed the presence of statistical heterogeneity among the studies by using the standard Cochran’s chi-square test, and the magnitude of heterogeneity by using the I^2 statistic. When statistical heterogeneity was present, we performed sensitivity analyses by omitting obvious outliers, and by conducting meta-analysis using the profile likelihood method”

- I do not specialize in conducting meta-analyses, however, to my understanding the I^2 statistics seem high throughout many of the meta-analyses from the various figures. Outlier omission was only done 2 or 3 times that I saw in the report. More detail regarding how heterogeneity was assessed and/or dealt with would seem important in light of the high I^2 s. Also, the testing of the subgroup interactions was not described.

Page 163+ **Line**

Tables 8 (p163) to Table 75 (p280)- It would be easier to navigate these tables if citation numbers were added so the reader can quickly ascertain what study is being referred to (there are many studies by the same authors, for some of the authors listed in the reference lists). This issue also pertains to the earlier Tables, including Tables 1 and 2.

Page 87 **Line**

Page 87-88: the summary descriptions reference the Figures, but should also probably reference the appropriate Tables from p163-280.

Page 87 ‘Pain Improvement from Baseline’- “There was no difference between epidural steroid injections and epidural non-steroid injections with anesthetic and or saline/water with respect to improvement in pain scores at short-term (Figure 3, 15 trials, mean difference -0.46 (95% CI: -0.97, 0.05)” .

- However, Figure 3 lists comparison groups including both ENSI and NEIs, in contrast to the quoted statement. I believe the same misstatement is made for other of the following

sentences from the paragraphs on p87-88 as well, corresponding to Figure 5, Figure 6, Figure 8, Figure 9, Figure 11, Figure 12, Figure 14, Figure 17, and so on.

Page 108 **Line**

There is a minor typo: "in one tria135,136l and".

There are several citation issues on this page

CONCLUSIONS Comments

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

- Are the conclusions reached valid?

Please see my comments above. This review was conducted with impeccable quality covering a vast range of the pain interventional literature. However, as stated above, based on conceptual grounds I do not believe that the 3 different epidural approaches are comparable sufficient to allow pooling of data, nor is pooling of non-fluoro guided interventions and fluoro-guided interventions. . Also, the combining of all outcomes <3 months seems inappropriate given that the expected duration of effect of ESI is likely substantially shorter for most patients. These issues is enough for me to question the validity of some of the efficacy-centered conclusions related to key question #1, including those pertinent to figures 3-29. That concern would be nullified if the results were broken out along the lines of ESI approach and fluoro guidance

The conclusions regarding key question #2 are valid, but should be separated by epidural type to have actual clinical or policy relevance

The conclusions for key questions #3 and #4 were largely not affected by pooling and are valid.

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 well structured and organized, and summarizes a tremendous amount of data concisely. It is relevant to clinical medicine and has policy indications. However, in the effort to distill much data into concise messages, too much combining of distinct procedural types has occurred, per my descriptions above. I believe this could be remedied by the simple suggestions described above, separating out various aspects of the data which have now been combined. From what I have seen reported here, this would likely not result in conclusions which are different for the overwhelming number of comparisons made, but those conclusions may be more valid.

QUALITY OF REPORT

Quality Of the Report

(Click in the gray box to make your selection)

Superior

Good

Fair

Poor

There are no gray boxes above to select. I would rate this report as superior regarding the technical and methodologic aspects of the review itself, excepting the decisions made with respect to pooling data for different procedures and with/without fluoro guidance.

This form was very hard to use. The sections listed in the form (Intro, background, key questions, methods, conclusions, etc) do not clearly correspond to sections in the 299-page document provided. The sections listed in the form might correspond to aspects of the Executive Summary, but that is only a small portion of this 300-page document.

Enter Form Comments Here

Email received from Pradeep Suri, Wednesday, February 10, 2016 7:36 AM

Dear Joe,

A thought occurred to me this week regarding my review sent last month, and a possible lack of clarity in one aspect of my comments.

My review recommends that the results of the meta-analysis not be combined by injection approach, or combine fluoro-guided vs. non-fluoro-guided injections, and I also suggested that the very short-term outcomes ≤ 1 month be separated out from the short-term > 1 to ≤ 3 months. In regards to these distinctions, although implied I likely should have stated more specifically that I believe these separations should pertain not only to the results, but to the summary of the results and the syntheses pertinent to the Executive Summary, table 1, and table 3- basically all areas where the results are presented and synthesized. The reason for this is because when the results are presented in a format where there is stratification according to subgroups, alongside a final pooling of all the subgroups, the tendency for readers is always to look at and draw conclusions based on the overall 'highest-order' meta-analysis. It is just human nature, especially for non-researchers. An example of this would be the many forest plots from the figures at the end of the review document, where the approach-specific meta-analysis are provided, alongside the all-approaches-combined meta-analysis included at the bottom of each forest plot. When presented in this way, the eye will always travel to the all-approaches-combined result whether or not it is appropriate to combine all injection approaches.

Perhaps this issue was already clear from my comments, but in case it was not, I wanted to relate this. My apologies that this is so late after I sent my review, and given the committee meeting this week.

Kind regards
Pradeep

Pradeep Suri M.D., M.S.
Associate Professor
University of Washington, Department of Rehabilitation Medicine
Staff Physician, Division of Rehabilitation Care Services, VA Puget Sound Health Care System
Investigator, Seattle Epidemiologic Research and Information Center (ERIC), VA Puget Sound Health Care System

PUBLIC COMMENTS**PUBLIC COMMENT #1: Gary Franklin, M.D., Office of the Medical Director, Washington State
Department of Labor and Industries**

Comments – L&I
January 14, 2016

Spinal injections (Re-review) draft evidence report

Office of the Medical Director, WA State Department of Labor and Industries

1. Page 5. Table 1. The strength of evidence of most of RCTs was downgraded to “low” or “insufficient”. It would be helpful to provide some specific information about quality of the RCTs to justify the rating.
2. Page 78. It may not be appropriate to group and pool the studies with different control injections (different substances), because the effect of an anesthetic injected into the epidural space, for example, is different from that of saline/water at least in a short term. The conclusion of a meta-analysis could be different if the substance in the control injections in the studies changes. In the meta-analysis on page 87 and Figure 6, the substances in the control injections were anesthetic and or saline/water, dry needling. It was concluded that “a greater proportion of patients receiving epidural steroid injections compared with epidural non-steroid injections (ENSI) with anesthetic and or saline/water achieved short-term successful pain relief defined as $\geq 20\%$, $\geq 50\%$ or 100% pain reduction (Figure 6), 11 trials, RR 1.30 (95% CI: 1.06, 1.58)”. Readers are not able to find out easily what control substance was used in each study from Figure 6 or the text. In addition, in the above meta-analysis, ESI in some studies contained not only steroid but also an anesthetic (*e.g.*, Cohen et al., 2012; Ghahreman et al, 2010; Manchikanti et al. 2012). This makes the matter even more complicated. The way of grouping comparators (control injections) makes it very difficult to draw appropriate conclusions. I wonder if you can separate the studies with different experimental injections (steroid alone or steroid + anesthetic) and different control injections (saline/water or anesthetic) in your meta-analysis.
3. Page 107. “Details on studies excluded after full text review are available in the Appendix C”. But Appendix C is not found in the document.
4. Page 281-299, Figure 3-24. The labels of “Favors ESI” and “Favors Control” in the Forest plots are very helpful. However, the placement of the labels in the plots is not consistent. For example, “Favors ESI” is on the left side of the plot in Figure 11, but it is on the right in Figure 12. It would be helpful to rearrange the Forest plots so that “Favors ESI” is either on the left or the right side throughout the report.

Email sent by Ian Zhao, Ph.D., Medical Program Specialist, Office of the Medical Director, Washington State Department of Labor and Industries, On Behalf of Gary Franklin, M.D.

PUBLIC COMMENT #2: Judith A. Turner, Ph.D., Janna Friedly, M.D., Bryan Comstock, M.S., Jeffrey G. Jarvik, M.D., M.P.H., University of Washington

As authors of the study (Turner, J., Comstock, B., Standaert, C., Heagerty, P., Jarvik, J., Deyo, R., Wasan, A., Nedeljkovic, S., Friedly, J.: Can patient characteristics predict benefit from epidural corticosteroid injections for lumbar spinal stenosis? *The Spine Journal*, 15:2319-2331, 2015) summarized in Table 4 in the section on lumbar stenosis: ESI vs. control injections, we would like to make the following comments:

1. We recommend adding a citation for each study listed in the table.
2. It is unclear to which study/studies the Table 4 footnotes 1 and 2 refer. We believe that the Table 4 footnotes would be more helpful if they were clearly linked to the relevant individual studies and more specific in terms of the issues relevant to bias in addressing the question of whether epidural corticosteroid injections are differentially effective for specific patient subgroups.
3. In our study, we intentionally examined a large number (21) of potential predictors and multiple (6) outcomes because we wanted to be exhaustive and comprehensive in our search. We did not find that any baseline patient characteristic consistently predicted differential response to epidural injections of corticosteroid plus lidocaine versus lidocaine only. We agree that caution is warranted in making conclusions about a single predictor that is found to be statistically significant when a large number of statistical tests are performed, given that significant relationships could be found by chance in this situation. Had we concluded that a baseline patient characteristic predicted benefit from epidural injections of corticosteroid, without correcting for multiple statistical tests, it would be reasonable to criticize that conclusion. However, despite performing a large number of tests examining 21 predictors and 6 outcomes, we did not find any characteristics that consistently indicated better response to corticosteroid plus lidocaine than to lidocaine only. We concluded in our article that, "Our findings do not support the existence of a specific subgroup of patients with lumbar spinal stenosis that is particularly responsive to epidural injections of corticosteroid + lidocaine versus lidocaine alone." Regardless of any correction for multiple testing that could be performed, our conclusions would be unchanged. Thus, we do not think that either criticism listed in the two Table 4 footnotes is relevant to our study. [Footnote 1: unclear whether the subgroup variables were specified a priori; the hypothesized impact of subgroup on treatment effect was not stated. Footnote 2: large number of subgroups tested (i.e., subgroup hypothesis not one of a smaller number tested); was unclear whether any of the subgroup variables were specified a priori; the hypothesized impact of subgroup on treatment effect was not stated.] We note here that we did select all potential predictors examined prior to conducting any statistical tests, and as we wrote in our article, "All tests were considered exploratory and hypothesis generating. Therefore, we did not adjust for the number of statistical tests because we did not want to increase the risk of false-negative findings. However, we acknowledge that this increases the potential for false-positive findings."
4. We point out that our study examined potential predictors of differential response to epidural injections of corticosteroid plus lidocaine versus lidocaine only. This study design does not address the question of which patients benefit from epidural injection of lidocaine plus corticosteroid versus placebo injections or other active treatment.

Judith A. Turner, PhD
Janna Friedly, MD
Bryan Comstock, MS

Jeffrey G. Jarvik, MD, MPH

University of Washington
Seattle, Washington

PUBLIC COMMENT #3: Steven R. Pollei, M.D., Medical Director, Center for Diagnostic Imaging, Federal Way and Lakewood, WA

January 14, 2016

Dorothy Teeter, Director
Washington State Health Care Authority
PO Box 42712
Olympia, WA 98504-2712

RE: Spinal Injections - Draft Evidence Report Comments

Dear Director Teeter:

Center for Diagnostic Imaging (COI) is a multi-state company providing subspecialized imaging and related services. We have 7 centers in the Greater Seattle area and are known for our high quality, patient focused care.

We appreciate the opportunity to comment upon the Spinal Injection Draft Evidence Report. In particular, we have concerns with the report's reliance upon data that fails to properly acknowledge the necessity of image guidance (fluoroscopy) in the delivery of epidural steroids. Indeed, the report suggests that fluoroscopy was utilized in only a handful (nine) of the 34 studies that were referenced in answering the many of the report's key questions. Further, it is unclear as to whether the studies that utilized fluoroscopy were separated from those that were conducted "blindly" in terms of efficacy or safety.

Fluoroscopy allows physicians to confirm whether the location of medication delivery via needle was accurate, increasing both the efficacy of the procedure and patient safety. Further, fluoroscopy can reveal anatomic derangements and abnormalities. Information regarding abnormalities is invaluable for determining the most efficient or the safest route for injection by the physician. Methods of "blind" injection, which this report appears to rely upon heavily, cannot confirm that the location of medication was accurate.

One study regarding epidural steroid administration found only a 30% rate of success (epidural penetration) in patients when performing needle placement "blind" (White et al.), while another study reported a 97.5% rate of success when performing epidural steroid administration under fluoroscopic visualization (El-Khoury et al.).

We would ask that the authors of the report re-consider its reliance upon studies that focused on techniques that are not the standard of care, much less in patients' best interest. Please let us know if you require more information or have any questions.

Sincerely yours,

Steven R. Pollei, M.D.
COI Medical Director,
Federal Way and Lakewood

Enclosure: Literature Citations and References

Literature Cited

- Bartynski, Walter S. et al. Incorrect Needle Position during lumbar Epidural Steroid Administration: Inaccuracy of loss of Air Pressure Resistance and Requirement of Fluoroscopy and Epidurography during Needle Insertion. American Journal of Neuroradiology. 2005; 26:502-505.
- El-Khoury G, Ehara S, Weinstein JN, et al. Epidural steroid injection: a procedure ideally performed with fluoroscopic control. Radiology 1988;168:554-557
- Fredman, Brian et al. Epidural Steroids for Treating 'Failed Back Surgery Syndrome': Is Fluoroscopy Really Necessary? Anesthesia and Analgesia Journal. 1999;88:367-72
- Johnson, Blake A, et al. Epidurography and Therapeutic Epidural Injections: Technical Considerations and Experience with 5334 Cases. American Journal of Neuroradiology. 1999;20:697-705
- White AH, Derby R, Wynne G. Epidural injections for the diagnosis and treatment of low back pain. Spine1980;5:78-86

PUBLIC COMMENT #4: Brandon Messerli, D.O., EvergreenHealth, Kirkland, WA

January 14, 2016

Dorothy Frost Teeter, Director
Washington State Health Care Authority
626 8th Avenue SE
P.O. Box 45502
Olympia, WA 98504-5502

Submitted via e-mail:
shtap@hca.wa.gov

Dear Ms. Teeter:

If one is interested in determining the effectiveness of a common and contemporary medical treatment, firstly a specific diagnosis must be chosen, secondly one identifies the current “gold standard” diagnostics to properly select subjects, and lastly a treatment is chosen specifically for that condition. In regards to the current practice of spinal injections, advanced imaging is nearly always necessary, and diagnostic blocks are mandatory in some cases, in securing a specific diagnosis. Only then can the optimal spinal injection treatment be administered. One example is that an acute foraminal disc herniation is approached by a transforaminal route for the epidural steroid injection. A caudal or interlaminar injection will not reach the site of pathology, and fluoroscopic guidance is an absolute requirement to ensure the target was achieved. A second example is that lumbar facet pain cannot be diagnosed without dual, concordant medial branch blocks having provided substantial pain relief, and is a requirement before proceeding with medial branch radiofrequency neurotomy using 18 or 20G electrodes in specifically defined target zones for a defined ablation time.

When performing a literature review regarding epidural steroid injections for lumbar radicular pain, it would be an error to include trials that lack methodological rigor. One would note that many older trials did not enroll subjects with imaging-confirmed pathology, and thus the injections were sometimes administered on subjects without the index condition. The heterogeneity of such studies precludes them from being helpful in answering the clinical question. One would also note that some trials did not choose an injection approach that ensures the injectate concentrates at the target, and some trials did not use imaging guidance at all. Data clearly shows that accuracy is unacceptably low if imaging guidance is not used. In either case, it is unknown if the injectate actually reached its target. Therefore, these studies are not helpful in answering the clinical question. Regarding outcomes data, one would note that results in this field are often bimodal rather than normally distributed; yet many studies only report continuous data rather than categorical data. The Ghahrman study (1) clearly demonstrated this fact; group mean data showed no benefit for ESI over the other study arms, but categorical data showed a significant and clear benefit. Of important note, this study and its categorical data was not included in Spectrum's evidence report, despite it being perhaps the most relevant study for ESI.

As a simile, imagine that the HTA reviews the effectiveness of azithromycin antibiotic treatment for community-acquired bacterial pneumonia. The key questions and evidence report allow for a review of RCTs assessing antibiotic treatment and cough. However, it failed to exclude trials that did not confirm the diagnosis with x-rays and cultures. Included studies thus included a heterogenous group of diagnoses, including viral and fungal pneumonia, hospital and nursing facility-acquired pneumonia, emphysema, asthma, heart failure, post-nasal drip, GERD, and cough due to ACE-inhibitor. Additionally, it failed to exclude studies that did not utilize the standard of care, such as azithromycin treatment for 5 days. Studies thus included a heterogenous group of inappropriate treatments, including 3 day antibiotic courses, IV antibiotics, and inappropriate use of penicillin in cases of penicillin-resistant bacteria or azithromycin for macrolid-resistant bacteria. It also failed to exclude studies that did not assess proper outcomes, such as resolution of cough or consolidation on x-ray at 3 and 6 weeks. The review also included studies that assessed continuous data. If half of subjects did not improve on antibiotics, because their cough was due to viral pneumonia or emphysema, then the mean data would show no significant benefit of antibiotic use.

This hypothetical systematic review pooled data from studies with a heterogenous group of diagnoses, treatments, and outcome measures. The evidence vendor's summary would state that the quality of evidence is low, and that antibiotics are not efficacious for treatment of cough. Clearly this conclusion is erroneous. A more appropriate approach would have been to assess the 1 or 2 clinical studies with optimal methodology for proper diagnosis, treatments consistent with current practice guidelines, and appropriate outcome measures.

It is unfortunate that the body of literature for spinal injections is not as consistently high-quality as one would hope. Fortunately, in the case of epidural steroid injections, there are several trials with methodology of very high quality, and these trials are certainly the best indicator of *current* clinical practice. These include the Ghahrman trial (1) that assessed categorical data, both Riew studies (2,3), and the Kennedy (4) and Kaufman (5) studies. The Kennedy (4) study is a prospective trial with optimal patient selection, injection technique, and outcomes data, and its results cannot be discounted simply because there was no placebo arm. An observational study by Kaufman (5) certainly has limitations due to its retrospective study design, but it must be considered since its methods utilized good patient selection, technique, and outcomes data, and it had a large sample size. The Ghahrman, Kennedy, and Kaufman studies were not included in Spectrum's review, so further analysis should be completed before the March 18th HTCC meeting. MacVicar's (6) systematic review of transforaminal ESI was not

reviewed in Spectrum's evidence report, but it should be reviewed by Spectrum as well, as it would be helpful in determining the methodological rigor of various studies.

In summary, a RCT with sound randomization, double blinding, and no losses to follow-up is of no value if the patients did not have the condition being studied and the procedure was not conducted accurately using contemporary techniques. As demonstrated by the example of antibiotic use for cough, stratification of studies by study methodology is of far greater importance.

For further reference regarding these issues, I have attached 5 correspondences for the HTCCs review. The draft LCD could be used as a template for the HTCC when determining coverage decisions. The Rathmell article highlights the safety profile of non-particulate steroid use for epidural injections.

1. The letter of September 15, 2015 from a multi-society pain workgroup to the HTA regarding the decision to re-review spinal injections.
2. The letter of December 15, 2014 from the International Spine Intervention Society to the AHRQ regarding the Draft Technology Assessment "Pain Management Injection Therapies for Low Back Pain".
3. Baker R. "Demystifying Lumbar Transforaminal Epidural Steroids: A Seminal Efficacy Study of a Specific Spinal Injection". *Pain Medicine* 2010; 11: 1141–1143.
4. Epidural Steroid Injections LCD Template from the Multi-Society Pain Workgroup.
5. Rathmell J. "Safeguards to Prevent Neurologic Complications after Epidural Steroid Injections Consensus Opinions from a Multidisciplinary Working Group and National Organizations". *Anesthesiology* 2015; XXX:00-00.

Sincerely,

Brandon Messerli DO
EvergreenHealth
Kirkland, WA

References:

1. Ghahreman A, et al. The efficacy of transforaminal injection of steroids for the treatment of lumbar radicular pain. *Pain Med* 2010;11:1149–68.
6. Riew KD, Park JB, Cho YS, et al. Nerve root blocks in the treatment of lumbar radicular pain. A minimum five-year follow-up. *J Bone Joint Surg Am* 2006;88:1722-5.
7. Riew KD, Yin Y, Gilula L, et al. The effect of nerve-root injections on the need for operative treatment of lumbar radicular pain. A prospective, randomized, controlled, double-blind study. *J Bone Joint Surg Am* 2000;82-A:1589-93.
8. Kennedy DJ, et al. Comparative effectiveness of lumbar transforaminal epidural steroid injections with particulate versus nonparticulate corticosteroids for lumbar radicular pain due to intervertebral disc herniation: a prospective, randomized, double-blind trial. *Pain Med.* 2014 Apr;15(4):548-55.
9. Kaufman T, et al. Clinical Effectiveness of Single Lumbar Transforaminal Epidural Steroid Injections. *Pain Medicine* 2013; 14: 1126–1133.

10. MacVicar J, King W, Landers MH, Bogduk N. The effectiveness of lumbar transforaminal injection of steroids: a comprehensive review with systematic analysis of the published data. *Pain Med* 2013;14:14
11. Tosteson AN, Skinner JS, Tosteson TD, et al. The cost-effectiveness of surgical versus nonoperative treatment for lumbar disc herniation over two years: Evidence from the Spine Patient Outcomes Research Trial (SPORT). *Spine* 2008;33:2108–15.
12. Karppinen J. Cost-effectiveness of periradicular infiltration for sciatica. Subgroup analysis of a randomized controlled trial. *Spine* 2001;26:2587–95.

Sent in a separate email, on behalf of the Multi-Society Pain Workgroup (MPW):

Josh Morse, MPH
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Submitted via e-mail: shtap@hca.wa.gov

Dear Josh,

I am writing in follow up to the correspondence the Health Technology Assessment has received from the Multi-Society Pain Workgroup (MPW). Letters were received on September 15, 2015 regarding the Draft Key Questions and on January 14, 2016 regarding the Draft Evidence Report. I am hopeful that the suggestions and comments have helped in the formulation of the Final Evidence Report. In brief, there was concern for the key questions regarding effectiveness being limited to only RCTs, inadequate subgroup analysis, and inappropriate weighting of trials without preference for sound technical methodology or categorical outcome reporting.

To assist the HTA and Spectrum with considering further references for analysis, and finalizing the report by February 12th, I have listed in this email (including attachments) clinical trials, systematic reviews, policy statements, and associated articles that were not included in the draft report. Of note, the referenced systematic reviews came to different conclusions than Spectrum because they appropriately included non-RCTs and weighted the trials based on design. Also included below are web links for the Medicare/Noridian interventional pain LCD policies currently in effect in Washington State.

It should be noted that in 2012 all CMS Contractor Medical Directors (CMDs) initiated a process to revise interventional spine LCDs so that they were consistent nationally. This was done as requested by Dr. Louis Jacques, director of the coverage and analysis group (CAG), in 2012. In 2013 the Office of the Inspector General (OIG) recommended "CMS establish a plan to evaluate new LCDs for national coverage", and this plan was endorsed by CMS administrator Dr. Tavenner.

Fourteen stakeholder specialty societies (the MPW), under the leadership of Drs. Ray Baker and Paul Dreyfuss, were convened by CMS to assist in the process of creating new nationally adopted LCDs. Expert consensus recommendations were based on a scientific, pragmatic, and a democratic process. Policy recommendations were formulated for epidural steroid injections, facet interventions, vertebroplasty and kyphoplasty, and spinal cord stimulation. Dr. Bernice Hecker, of Noridian Healthcare Solutions, was the lead CMD in this effort to create consistent national LCDs. She wrote of this process: "...the CMDs and MPW have developed a wonderful process for the development of coverage determinations that promote best practices and patient well-being. We have gathered the best minds and hearts in the country who volunteer their time and in-depth niche expertise to ensure patients are cared for in the best possible manner."

Noridian, Washington States regional carrier, was the first carrier to update their interventional pain LCD policies based on the recommendations of the MPW, and other carriers have subsequently created new LCDs as well.

I am hopeful that this tremendous body of work, culminating in Noridian's LCD, will be of utility for the HTCC when determining coverage policies for the HCA. We trust that the HTCC will uphold the Washington Administrative Code 182-55-035, which states:

- (2) Identify whether the determination is consistent with the identified medicare decisions and expert guidelines.
- (3) For decisions that are inconsistent with either the identified medicare decisions or expert guidelines, specify the reason(s) for the decision and the evidentiary basis.

Thank you for your consideration.

Thank you for your consideration.

Sincerely,

Brandon Messerli, DO
EvergreenHealth
Staff Physician

References

Lumbar Transforaminal ESI

Clinical Trials:

Kennedy DJ, et al. Comparative effectiveness of lumbar transforaminal epidural steroid injections with particulate versus nonparticulate corticosteroids for lumbar radicular pain due to intervertebral disc herniation: a prospective, randomized, double-blind trial. *Pain Med.* 2014 Apr;15(4):548-55.

Kaufman T, et al. Clinical Effectiveness of Single Lumbar Transforaminal Epidural Steroid Injections. *Pain Medicine* 2013; 14: 1126–1133.

Systematic Review:

MacVicar J, King W, Landers MH, Bogduk N. The effectiveness of lumbar transforaminal injection of steroids: a comprehensive review with systematic analysis of the published data. *Pain Med* 2013;14:14

ESI Safety

Clinical Trial:

El-Yahchouchi CA, Plastaras CT, et al. Adverse Event Rates Associated with Transforaminal and Interlaminar Epidural Steroid Injections: A Multi-Institutional Study. *Pain Med.* 2015 Nov 23.

SI Joint

Clinical Trials:

Liliang PC, Lu K, Weng HC, et al. The therapeutic efficacy of sacroiliac joint blocks with triamcinolone acetonide in the treatment of sacroiliac joint dysfunction without spondyloarthropathy. *Spine* 2009;34:896–900.

Maugars Y, et al. Assessment of the efficacy of sacroiliac corticosteroid injections in spondylarthropathies: A doubleblind study. *Br J Rheumato* 1996;35:767–70.

Systematic Review:

Kennedy DJ, Engel AJ, Kreiner DS, Nampiaparampil D, Duszynski B, MacVicar J. Fluoroscopically guided diagnostic and therapeutic sacroiliac joint injections: a systematic review. *Pain Med* 2015; 16: 1500-1518.

Facet joint

Clinical Trials:

Ackerman WE, Ahmad M. Pain relief with intraarticular or medial branch nerve blocks in patients with positive lumbar facet joint SPECT imaging: a 12-week outcome study. *South Med J*. 2008 Sep;101(9):931-4.

Dolan AL, Ryan PJ. The value of SPECT scans in identifying back pain likely to benefit from facet joint injection. *Br J Rheumatol*. 1996 Dec;35(12):1269-73.

Pneumaticos SG, Chatziioannou SN. Low back pain: prediction of short-term outcome of facet joint injection with bone scintigraphy. *Radiology*. 2006 Feb;238(2):693-8.

Policies

Noridian ESI LCD for Washington State:

[https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34980&ContrId=358&ver=2&ContrVer=1&CntrctrSelected=358*1&Cntrctr=358&name=Noridian+Healthcare+Solutions%2c+LLC+\(Noridian+Healthcare+Solutions%2c+LLC+\(02402%2c+A+and+B+MAC%2c+J+-+F\)\)&LCntrctr=358*1&DocType=Active&bc=AAAAAAIAAAAAAA%3d%3d&](https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34980&ContrId=358&ver=2&ContrVer=1&CntrctrSelected=358*1&Cntrctr=358&name=Noridian+Healthcare+Solutions%2c+LLC+(Noridian+Healthcare+Solutions%2c+LLC+(02402%2c+A+and+B+MAC%2c+J+-+F))&LCntrctr=358*1&DocType=Active&bc=AAAAAAIAAAAAAA%3d%3d&)

Noridian Facet Joint LCD for Washington State:

[https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34995&ContrId=358&ver=14&ContrVer=1&CntrctrSelected=358*1&Cntrctr=358&name=Noridian+Healthcare+Solutions%2c+LLC+\(Noridian+Healthcare+Solutions%2c+LLC+\(02402%2c+A+and+B+MAC%2c+J+-+F\)\)&LCntrctr=358*1&DocType=Active&bc=AAAAAAIAAAAAAA%3d%3d&](https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34995&ContrId=358&ver=14&ContrVer=1&CntrctrSelected=358*1&Cntrctr=358&name=Noridian+Healthcare+Solutions%2c+LLC+(Noridian+Healthcare+Solutions%2c+LLC+(02402%2c+A+and+B+MAC%2c+J+-+F))&LCntrctr=358*1&DocType=Active&bc=AAAAAAIAAAAAAA%3d%3d&)

Articles

Rathmell JP, Benzoni HT, et al. Safeguards to prevent neurologic complications after epidural steroid injections: consensus opinions from a multidisciplinary working group and national organizations. *Anesthesiology*. 2015 May;122(5):974-84.

Maus T. AHRQ on the Draft Technology Assessment “Pain Management Injection Therapies for Low Back Pain” Comments Submitted Fall 2014.

Baker R. Demystifying Lumbar Transforaminal Epidural Steroids: A Seminal Efficacy Study of a Specific Spinal Injection. *Pain Medicine* 2010; 11: 1141–1143.

Multi-Society Pain Workgroup Recommendations on Interventional Pain Local Coverage Decisions.

Department of Health and Human Services Office of Inspector General. LCD Determinations Create Inconsistency in Medicare Coverage. Jan 2014.

Belinda Duszynski, Senior Director of Policy and Practice at the Spine Intervention Society

January 14, 2016

Josh Morse, MPH
Health Technology Assessment Program Director
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Submitted via e-mail: shtap@hca.wa.gov

Dear Mr. Morse: Representatives of 15 medical specialty societies, comprising physicians who utilize and/or perform spinal injection procedures to accurately diagnose and treat patients suffering from spine pathologies, have convened to review and comment on the draft report from the Washington State Health Care Authority's (WA HCA) Health Technology Assessment Program's re---review of spinal injections. These medical specialty societies share a common goal with the WA HCA: identifying spinal injections that provide value to the patient and society through measurable improvements in pain and physical functioning with no or minimal adverse events.

We extend to the committee an offer to provide national and international expert input as a resource for this process. We are fully cognizant of the issues of cost---containment, overutilization and inappropriate utilization, and therefore also wish to bring into focus which interventions are effective when treating the various causes of back and neck pain. We have concerns, however, that because of the questions posed, along with the review's inclusion/exclusion criteria, the report will not assist in making such determinations. In fact, the report's conclusions may lead to egregious denial of access to these procedures for many patients suffering from spine pathology.

In the spirit of transparency, it is imperative that the WA HCA request the authors of the report carefully consider all comments received during the public comment period, and require that a document outlining all comments and how they have been addressed be made publicly available with the final report. We trust that due consideration will be given to our comments and that the report will be revised to ensure that all of the highest quality evidence is addressed in order to provide an accurate assessment of the procedures reviewed.

Our primary concerns fall into these main categories:

- Topic Selection
- Report Development Methodology
 - Absence of Peer-Review Process
- Evidence Base Restriction to Randomized Controlled Trials (RCTs)
- Inadequate Subgroup Analyses for Each Question
 - o Specific Diagnoses o Image Guidance
 - o Approach/Access/Accuracy
- Statistical Analysis: Inappropriate Weight to Continuous (Mean) Data
- Accuracy of Data Presentation and Conclusions
- General Public Health Concerns

Topic Selection

We question the decision to re-review the entire field of spinal injection based upon publication of one new study by Friedly *et al.* (1) and a U.S. Food and Drug Administration initiative to assess the risk of epidural steroid injections (2). In regards to the former, this clinical study did not pertain to the majority of spine pathologies, including: lumbar foraminal or lateral recess stenosis, lumbar disc herniations and radicular pain, facet or sacroiliac joint pain, or any cervical or thoracic pathology. Thus, there is no basis for a re-review of the efficacy concerning these conditions and their associated treatments, nor is there new evidence that would warrant a reversal of the coverage decisions made by the WA HCA Health Technology Clinical Committee (HTCC) in 2011.

In regards to the FDA initiative, similar to nearly all medical treatments, there are known potential risks with epidural steroid injections. The most serious and lasting complications include spinal cord infarction or direct injury, brainstem and brain infarction, and spinal nerve root injury. The FDA's concerns were raised on the basis of case reports – low quality evidence inappropriate for formulating practice recommendations. These reports were published prior to the 2011 WA HCA review of spinal injections, and were therefore considered in the 2011 WA HCA report's safety discussion. In fact, the only new data available are from large studies showing safety of spinal injections. A recently published multi-institutional study examined more than 16,500 consecutive epidural injections performed in accordance with evidence-based guidelines in all spine segments with no major adverse events. (3)

An expert working group with facilitation from the FDA's Safe Use Initiative (SUI) and representatives from leading specialty societies reviewed the existing scientific evidence and assembled consensus clinical considerations aimed at reducing the risk of severe neurologic complications. (4) The working group and the advising national organizations unanimously agreed that epidural injections of steroids were rarely associated with serious complications due to injuries of the central nervous system. They agreed that transforaminal injections are associated with a risk of catastrophic neurovascular complications and that particulate steroids appear to be inordinately represented in case reports of these complications. The representatives unanimously approved the clinical consideration that only non-particulate steroids should be used in therapeutic cervical transforaminal injections. Although use of non-particulate steroid dexamethasone as a first-line injectate in lumbar transforaminal injections was recommended, the representatives unanimously agreed that there might be instances where particulate steroids could be used in this setting (e.g., a patient fails to improve after an initial treatment with non-particulate steroid). Clinical considerations involving technical aspects of the procedures included the necessary use of appropriate image-guided views, injection of contrast under real-time fluoroscopy, review of prior imaging studies, use of facemask and sterile gloves, use of extension tubing, and avoidance of heavy sedation. Spinal injections should not be abandoned due to a very low risk of neurologic injury, particularly when appropriate measures can and should be utilized to substantially mitigate risks. Ultimately, the FDA has not modified the Black Box warning or limited use of corticosteroid for epidural steroid injections.(5)

Report Development Methodology

Spectrum Research is a for-profit company that has been contracted to perform at least 14 separate health technology assessments for the state of Washington. Given the established financial relationship between the two parties, and potential for reciprocity in the form of ongoing contracts which could be construed as a conflict of interest, at the very least the report itself should disclose this relationship between the two parties.

The WA HCA website indicates that clinical experts may be consulted at various points throughout the HTA process. The clinical experts serving in any advisory role for the review must be intimately familiar with the intricacies of proper patient selection and study design, technical 'nuances' of proper injection techniques, and the utility of various outcome measures. The process for selecting these experts needs to be rational and transparent. Experts should be highly regarded among their peers in the field of interventional pain management. While the report indicates that a number of experts in various fields participated in this review, the lack of transparency about their names, expertise, and level of involvement is of concern. Involvement of individuals with subject-specific clinical expertise in the development of the report is critical.

Washington State law RCW 70.14.110 states that the HTCC's decision cannot differ from Medicare or expert guidelines unless there is substantial evidence that their coverage decisions are wrong. Despite this requirement, the report failed to outline Medicare's coverage policies (e.g. Noridian's local coverage determinations on spinal injection procedures) or review expert guidelines published by the national medical societies vested in these treatments, such as those providing these comments. It would be prudent for the HTCC to review these policies and guidelines, as they would provide assistance in determining coverage decisions, and it is necessary to ensure that state law is followed.

Based on that state law, to restrict access to spinal injections, the burden of proof thus lies with the HTCC to prove these interventions are no better than placebo. Of the 142 conclusions reached, only two were based on high quality evidence, and these pertained to epidural steroid injections compared with epidural injections of local anesthetic in the treatment of one condition, lumbar central stenosis. (6) Only three conclusions were based on moderate quality evidence. There are 137 conclusions with low or insufficient evidence. When interpreting these conclusions, it is imperative that "low quality evidence" is not equated to "low treatment efficacy".

Absence of Peer Review Process

According to the report, "the information in this assessment is intended to assist health care decision makers, clinicians, patients and policy makers in making sound evidence-based decisions that may improve the quality and cost-effectiveness of health care services." Peer-reviewed journals are meant to serve this purpose, as their editors are clinical and research experts who review manuscripts and approve publications only of the highest quality and ensure the absence of bias. It is of great concern that this technology assessment, which has bypassed the typical peer-review process by clinical experts, will be used to inform decisions that will potentially affect the care of millions of patients in the United States.

Evidence Base Restriction to Randomized Controlled Trials (RCTs)

Evidence-based medicine seeks to identify the "current best evidence", including clinical evidence, in making patient care decisions. (7) With a restriction to randomized controlled trials (RCTs) as the sole evidence to address questions of efficacy, the report ignores the **best available** evidence. The exclusion of high quality observational studies of clinical effectiveness removes important information and context from a synthesis of the literature. (7-9) In the recently published systematic review of long-term opioid therapy for chronic pain, Chou *et al.* highlighted the importance of observational studies in situations where RCTs fail to adequately assess effectiveness with consideration to important factors, such as type of pain and patient characteristics. (10,11) "Observational studies could also help address a number of these research questions, but should be specifically designed to evaluate patients with chronic pain prescribed long-term opioid therapy and appropriately measure and address potential confounders." (10)

Recent methodology literature suggests that effect estimates from high quality observational trials do not differ significantly from RCTs. (9) Many of the RCTs that met the inclusion criteria established by the authors of this report include patients selected only by symptoms or in whom image guidance has not been utilized. These failings, further discussed below, make such trials irrelevant to current clinical practice and not unexpectedly show poor outcomes. Comparing non- image guided (blind) injections to injections performed in accordance with evidence-based guidelines (12) that achieve precise needle placement at a 1-2mm target zone in three- dimensional space with confirmation of medication distribution by real-time observation of contrast flow has no validity. There are very few RCTs that utilize current practice standards. Hence, examination of recently published large observational studies adds important information that is more relevant to current standards of practice.

There is no mandate by the WA HCA to limit technology assessments to RCTs. The choice to limit the review to RCTs was purposeful and inconsistent with prominent ideology regarding evidence- based medicine. (7) Evidence-based medicine involves identifying the best available evidence with which to answer clinical questions. An observational trial with appropriately selected patients and treatment indications, accurate and current treatment techniques, and appropriate outcome measures and time frames is far more relevant than an RCT with good randomization and blinding, but improper patient and treatment indications, antiquated or poor treatment technique, and weaker outcome measures.

If all RCTs are analyzed as equals, simply because they have good randomization and low risk of bias, this does a great disservice to the scientific gains and practice improvements that the field of spine medicine has achieved in the last several decades. As an analogy, consider a hypothetical review of RCTs involving chemotherapy for breast cancer, spanning several decades of research, in which all of the studies were considered equivalent and pooled data were utilized. The efficacy of current diagnostic and treatment paradigms would appear erroneously poor, despite the clear gains this field has achieved in recent decades and years.

Purposefully preventing a comprehensive and unrestricted evidence-based review is a great disservice to all stakeholders, as the review will come to erroneous conclusions, and the HTCC could egregiously deny access to procedures that truly can be beneficial. The ramifications of this cannot be understated. Patients could be left to suffer in pain; become dependent on risky and expensive medications; seek unnecessary, risky, and expensive surgeries; utilize additional health care resources; miss more work and incur time-loss payments and/or loss of taxable income; and other far-reaching consequences.

Inadequate Subgroup Analyses for Each Question:

Specific Diagnosis

We commend the authors of the report on making an attempt to define appropriate subgroups/diagnoses; however, the categories implemented (e.g. lumbar radiculopathy due to disc pathology and/or foraminal narrowing, lumbar radiculopathy attributed to multiple causes) represent a mixed bag of anatomic diagnoses, clinical syndromes without defined pathology, and inappropriate grouping of distinct diagnoses. The categories fail to adequately represent the way anatomic pathology and clinical presentation of symptoms are evaluated both clinically and in the literature.

In the fields of interventional spine injections and surgery, it is imperative to secure an exact diagnosis before proceeding with a specific treatment. Clinical history-taking and physical examination alone have been proven to insufficiently elicit an exact diagnosis, and therefore the proper treatment remains

unknown. Advancements in imaging provide substantial insight into anatomic pathology, and together with a history, examination, and sound medical judgment, will lead to a definitive diagnosis. Only then can a specific spinal intervention be offered and performed. Despite this necessity, several of the RCTs that met inclusion criteria for this report did not require advanced imaging to secure a diagnosis. Some of these trials are older studies that either did not have such advanced imaging at their disposal or were performed at a time when standard of care did not require imaging.

It is critical to perform subgroup analyses by specific diagnoses. For example, there is no physiologic process beyond systemic effect by which steroids delivered to the epidural space would be expected to relieve axial back pain arising from nociception in the intervertebral discs, facet joints, sacroiliac joints, or supporting musculature. There is ample experimental and clinical evidence that radicular pain has an inflammatory basis and is potentially susceptible to targeted delivery of an anti-inflammatory agent to the interface of neural tissue and the compressive lesion. (13) For this reason, it is imperative that studies included in the assessment have diagnostic specificity, with correlative imaging findings as a requirement for inclusion.

As an analogy, consider a hypothetical systematic review of prescription medication for the treatment of cough, a common symptom like low back pain. Studies may show beneficial effects from antibiotics in a group of patients with bacterial pneumonia, a specific diagnosis, whereas pooled data from heterogeneous groups of patients with cough – including viral bronchitis, chemical pneumonitis, asthma, lung cancer, *etc.* – would produce different effects. If these pooled effects showed that many different medications had minimal impact on cough from various sources, would we abandon prescription antibiotics for pneumonia?

Additionally, the identification of the underlying etiologies of pain is essential as different pathologies not only have varying responses to treatment, but also have different natural histories, impacting prognosis. Thus, the time frame of follow-up to determine clinical utility becomes imperative. Some conditions, such as intervertebral disc herniation, can result in debilitating pain, but have an overall favorable natural history. This would be in contrast to neurogenic claudication due to central canal stenosis, which is less likely to resolve spontaneously with time. Thus short-term relief would be very appropriate and expected for pain caused by a disc herniation. To evaluate the long-term effects in this population would be as flawed as evaluating the long-term effectiveness of antibiotics for pneumonia. Again, should we withhold all antibiotics for pneumonia given the largely favorable natural history, or should we state antibiotics are ineffective because all subjects were better at 1 year follow-up? Similarly, should we withhold pain medications from patients with fractures or after orthopedic surgery, as these conditions only result in pain and have favorable natural histories?

Imaging Guidance

The techniques utilized in the administration of epidural steroids are also critical. The authors of the report acknowledge that the use of image guidance was reported in only two of the studies of interlaminar epidural steroids for lumbar radiculopathy. However, they fail to separately analyze results based upon use of image guidance. Furthermore, while they state that image guidance is often used to improve accuracy of medication delivery, they do not acknowledge the impact of image guidance on outcomes. Data show that “epidural” injections performed without image guidance may not universally reach the epidural space, even in expert hands. (14-16) Off-target medication delivery may not be efficacious and may be dangerous. The report directly contradicts the FDA Safe Use Initiative on epidural steroid injections that demands image guidance. (4) To suggest to patients and physicians that epidural steroid injections do not require image guidance may create a significant potential for patient harm.

Approach, Access, Accuracy

While image guidance is essential, the technique of delivery is equally important. As with image guidance, the authors acknowledge that different approaches to the epidural space exist. While data are presented by different approach in the tables, the text and conclusions pool results from the various approaches together. Many midline interlaminar epidural steroid injection (ILES) and caudal injection studies suffer from the lack of image guidance; and even when performed with image guidance, these procedures may deliver medication distant from the site of pathology, without certainty that the steroid will reach, or in what concentration it will reach, the target zone in the ventral epidural space. In contrast, transforaminal epidural steroid injection (TFESI) procedures place the needle in direct proximity to the target nerve and verify delivery to that site by observing contrast media flow. (17) Recently described lateral parasagittal ILES have also been shown to preferentially deliver injectate to the target ventral epidural space. (18) It is not reasonable to combine these different injection techniques in an evaluation of “epidural steroid injections”.

Many studies have shown that technically accurate injections will produce better outcomes. The only way to control for technical accuracy in a clinical trial is with blinded analysis of all procedure images and contrast media spread by independent reviewers. This has not been done in any of the studies included in the current report.

Statistical Analysis: Inappropriate Weight to Continuous (Mean) Data

Many of the included RCTs report only continuous data as a comparison between group means in reference to a minimum clinically important difference. However, pain and functional disability treatment responses are rarely normally distributed. Rather, responses are often bimodal, with segregation into responder and non-responder populations. Group means will thus conceal a clinically significant response in the responders. Categorical outcomes that define the proportion of patients reaching a predefined responder status are critical to meaningful interpretation, as noted in the recent NIH Task Force recommendations on research standards for chronic low back pain. (19) Given the importance of relying on categorical data, acknowledged by the report’s authors, it is disappointing that the categorical data from the Ghahreman, *et al.* study were not included in the review. (20) When categorical data are available, they should be acknowledged and greater weight should be applied to these results than studies with mean data.

Accuracy and Transparency of Data Presentation and Conclusions

The stated aim of the report was to, “systematically review, critically appraise, analyze, and synthesize research evidence evaluating the efficacy, comparative efficacy, and safety of spinal injections in adults with subacute or chronic spinal pain.” Of the 142 conclusions reached, only five were rated “high quality”. This extensive document can only say very few things with any amount of certainty. One certain conclusion is that there is no difference between epidural steroid and epidural anesthetic in achieving short-term pain relief in the treatment of lumbar stenosis. It is unfortunate if this entire report was commissioned to make this one recommendation based on the “new literature” identified, namely the LESS trial by Friedly, *et al.* (1) Surprisingly, two of the other recommendations graded “moderate” or higher are in support of intra-articular facet steroid injections. This is despite a relative dearth of evidence in support of this procedure.

This is in stark contrast to a number of high quality peer-reviewed systematic reviews on similar topics that have been able to arrive at significant conclusions. In the author’s literature search for such reviews, they failed to identify arguably the best reviews on epidural steroid injections for lumbar and cervical radicular pain by MacVicar, *et al.* and Engel, *et al.* respectively. (21-23) The tabulation of grading

appears to give a semblance of transparency in the evaluation of a group of studies, but these data tables are far from transparent. Some examples of issues with the tables include the following:

- 8) The individual papers comprising the sub-analysis for each subject in each table are not cited. Without appropriate referencing, it appears that RCTs may have been missing from the analyses in several tables. For transparency sake, it is critical to identify the studies.
- 9) A uniform definition of the various outcomes has not been provided across all tables. Successful outcomes should be clearly defined for all categories in all tables.
- 10) There are inconsistent analyses across categories by duration of follow-up (e.g. combining intermediate and long-term in some categories and not others).
- 11) There is not uniformity in the tables for reporting all outcomes data at each time point. It appears the authors have arbitrarily selected outcomes and time points as was seen fit, rather than uniformly listing studies in all categories.
- 12) If evaluating facetogenic pain, the data presentation should be comprehensive. It is unclear why sacroiliac pain is omitted from Table 1.
- 13) There is obviously a risk differential between cervical and lumbar interventions, the types of interventions, and the injectates utilized. The grading of studies in Table 3 does not take this into account, but lumps them altogether.
- 14) Transparency is required in delineating how the authors have reached the conclusions. "ESI for disc and foraminal compression" simply states "no significant difference" and "low quality evidence". Without additional explanation, the assessment appears arbitrary.

Meaningful conclusions cannot be derived without re-analyzing the data after excluding all RCTs in which no confirmatory imaging was done or reported, no fluoroscopic guidance was used (most old studies), and no caudal epidural steroid injections were allowed. This analysis should also stratify results of each treatment by diagnosis [e.g. TFESI for acute/subacute pain, TFESI for acute single-level HNP, TFESI for low-to-moderate grade compression, *etc.*].

General Public Health Concerns

A systematic review of a specific topic is not required to take into consideration a plethora of other factors that are prudent when a physician and patient decide to pursue a treatment. On the other hand, a committee making coverage decisions does need to consider the bigger picture. Some patients may have no other options apart from spinal injections. Implicit in this discussion of spinal injections is that conservative care (e.g. physical therapy, chiropractic, medications, *etc.*) has failed. Surgery can be contraindicated due to comorbidities or age, and some patients are adamant that they want to avoid surgery at all costs. Surgery also entails the very real risks of immediate or delayed surgical failure, technical failure, serious infections, permanent paralysis, re-herniations, and subsequent segmental instability requiring fusion. Several authors reported significantly worse outcome of discectomy in those with small, contained disc herniation. (24-26) Some even excluded from surgical consideration patients with small size lumbar disc herniation. (27) Thus, for patients with radicular pain because of a small disc herniation, surgery is far from a guaranteed solution. These are relevant considerations in the broader scope of clinical decision-making between a patient and physician.

Chronic or palliative care is also not always a good option. Opioids and NSAIDs can be contraindicated due to comorbidities, and both may have only short-term and minimal benefits. A large, utilization review, conducted in Denmark, of 2,000 patients who used opioids long-term for chronic pain, found that opioid therapy failed to fulfill any of the treatment goals: pain relief, improved quality of life, or

improved functional capacity. (28) Long-term opioid therapy has very real and serious adverse effects, such as physical dependence, tolerance, opioid-induced pain hyperalgesia, addiction, diversion, and abuse; and side effects such as impairment of the immune, endocrine, and reproductive systems. (29-32) Increasing abuse and diversion of prescription opioids have become a serious problem. According to the Centers for Disease Control and Prevention (CDC), during 2014, 28,647 (61%) drug overdose deaths involved some type of opioid, including heroin. Prescription opioids killed 19,000. (33)

Regarding NSAIDs, a study in the *New England Journal of Medicine* estimated that at least 103,000 patients are hospitalized per year in the United States for serious gastrointestinal complications due to NSAID use. (34) At an estimated cost of \$15,000 to \$20,000 per hospitalization, the annual direct costs of such complications exceed \$2 billion. This study also estimated that 16,500 NSAID-related deaths occur every year in the United States. This figure is similar to the annual number of deaths from AIDS and considerably greater than the number of deaths from asthma, cervical cancer or Hodgkin's disease. NSAIDs can be considered to be the 15th most common cause of death in the US.

There is no doubt that spinal injections are not the panacea for all spinal conditions. There are conditions best treated conservatively and others best treated surgically. Spinal injections provide a valuable alternative option for some people. And unlike some medical treatments, which “cure” a problem (e.g. appendectomy), many spinal conditions cannot be cured. Repetitive, palliative treatments can be the only option. The risk-benefit ratio of repeated spinal injections can sometimes be preferable to perpetual medication use, or simply living with pain and disability.

Summary

It is imperative to recognize that study methodology is meaningless unless the procedures being assessed are performed on appropriately selected patients with appropriate indications using accurate and current technique. An RCT with sound randomization, excellent blinding, and no losses to follow-up is of no value if the patients did not have the condition under investigation and/or the therapeutic procedure was not conducted accurately. Stratification of studies by appropriate patient selection and acceptable, technical performance of the procedures is critically important and must be considered in parallel with, or even precede, evaluation of study design in assigning value to a study. Because the methodological limitations outlined above, the current draft of the report does not adequately address the key questions posed and is not a satisfactory reference for the topic.

Thank you for considering our comments, which are offered in the spirit of collaboration to ensure an accurate assessment of injection procedures that can be effective tools in the treatment of appropriately selected patients. 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@spinalinjection.org.

Sincerely,

American Association of Neurological Surgeons
American Academy of Pain Medicine
American Academy of Physical Medicine and Rehabilitation
American College of Radiology
American Pain Society
American Society of Anesthesiologists
American Society of Neuroradiology

American Society of Regional Anesthesia and Pain Medicine
American Society of Spine Radiology
Congress of Neurological Surgeons
North American Neuromodulation Society
North American Spine Society
Society of Interventional Radiology
Spine Intervention Society
Washington State Association of Neurological Surgeons

References:

1. Friedly JL, Comstock BA, Turner JA, et al. A randomized trial of epidural glucocorticoid injections for spinal stenosis. *N Engl J Med* 2014;371:11---21.
2. FDA Drug Safety Communication: FDA requires label changes to warn of rare but serious neurologic problems after epidural corticosteroid injections for pain. April 23, 2014.
<http://www.fda.gov/Drugs/DrugSafety/ucm394280.htm>
3. El---Yahouchi CA, Plastaras CT, Maus TP, Carr CM, McCormick ZL, Geske JR, Smuck M, Pingree MJ, Kennedy DJ. Adverse event rates associated with transforaminal and interlaminar epidural steroid injections: A multi---institutional study. *Pain Med*. 2015 Nov 23. [Epub ahead of print]
4. Rathmell JP, Benzon HT, Dreyfuss P, Huntoon M, Wallace M, Baker R, Riew KD, Rosenquist RW, Aprill C, Rost NS, Buvanendran A, Kreiner DS, Bogduk N, Fourney DR, Fraifeld E, Horn S, Stone J, Vorenkamp K, Lawler G, Summers J, Kloth D, O'Brien D, Tutton S. Safeguards to prevent neurologic complications after epidural steroid injections: consensus opinions from a multidisciplinary working group and national organizations. *Anesthesiology*. 2015 May;122(5):974---84.
5. Racoosin JA, Seymour SM, Cascio L, Gill R. Serious neurologic events after epidural glucocorticoid injection-----the FDA's risk assessment. *N Engl J Med*. 2015 Dec 10;373(24):2299--- 301.
6. Bicket MC, Gupta A, Brown CH, Cohen SP. Epidural injections for spinal pain: a systematic review and meta---analysis evaluating the "control" injections in randomized controlled trials. *Anesthesiology* 2013;119:907---31.
7. Sackett, D. L., Rosenberg, W. M. C., Gray, J. A. M., Haynes, R. B. & Richardson, W. S. Evidence based medicine: what it is and what it isn't. *BMJ* 1996;312,71---72.
8. Concato, J., Shah, N. & Horwitz, R. I. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *NEJM* 2000;342:1887---1892.
9. Anglemeyer A, Horvath HT, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. *Cochrane Database Syst Rev*. 2014 Apr 29;4:MR000034.
10. Chou R, Deyo R, Devine B, Hansen R, Sullivan S, Jarvik JG, et al. The Effectiveness and Risks of Long---Term Opioid Treatment of Chronic Pain. Evidence report/technology assessment no. 218. (Prepared by the Pacific Northwest Evidence---based Practice Center under contract no. 290---2012---00014---I). AHRQ publication no. 14---E005---EF. Rockville, MD: Agency for Healthcare Research and Quality; 2014.
11. Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I, Dana T, Bougatsos C, Deyo RA. The effectiveness and risks of long---term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med*. 2015 Feb 17;162(4):276---86.
12. Bogduk N ed. Practice guidelines for spinal diagnostic and treatment procedures. 2nd edition. International Spine Intervention Society. San Francisco, USA 2013.
13. Mulleman D, Mammou S, Griffoul I, Watier H, Goupille, P. Pathophysiology of disk---related sciatica. I. Evidence supporting a chemical component. *Joint Bone Spine* 2006;73(2):151---8.
14. Sharrock NE. Recordings of, and an anatomical explanation for, false positive loss of resistance during lumbar extradural analgesia. *Br J Anaesth*. 1979 Mar;51(3):253---8.

15. Bartynski WS, Grahovac SZ, Rothfus WE. Incorrect needle position during lumbar epidural steroid administration: inaccuracy of loss of air pressure resistance and requirement of fluoroscopy and epidurography during needle insertion. *AJNR Am J Neuroradiol* 2005; 26 (3): 502---5.
16. White AH, Derby R, Wynne G. Epidural injections for the diagnosis and treatment of low---back pain. *Spine (Phila Pa 1976)* 1980 Jan---Feb; 5 (1): 78---86.
17. Ackerman WE, 3rd, Ahmad M. The efficacy of lumbar epidural steroid injections in patients with lumbar disc herniations. *Anesth Analg*. 2007 May;104(5):1217---22
18. Ghai B, Vadaje KS, Wig J, Dhillon MS. Lateral parasagittal versus midline interlaminar lumbar epidural steroid injection for management of low back pain with lumbosacral radicular pain: a double---blind, randomized study. *Anesth Analg* 2013; 117 (1): 219---27.
19. Deyo RA, Dworkin SF, Amtmann D, Andersson G, Borenstein D, Carragee E, Carrino J, Chou R, Cook K, DeLitto A, Goertz C, Khalsa P, Loeser J, Mackey S, Panagis J, Rainville J, Tosteson T, Turk D, Korff MV, Weiner DK. Report of the NIH Task Force on research standards for chronic low back pain. *Pain Med* 2014; 15 (8): 1249---67.
20. Ghahreman A, Ferch R, Bogduk N. The efficacy of transforaminal injection of steroids for the treatment of lumbar radicular pain. *Pain Med* 2010;11(8):1149---68.
21. MacVicar J, King W, Landers MH, Bogduk N. The effectiveness of lumbar transforaminal injections of steroids: a comprehensive review with systematic analysis of the published data. *Pain Med* 2013; 14: 14--28.
22. Engel A, King W, MacVicar J. The effectiveness and risks of fluoroscopically---guided cervical transforaminal injections of steroids: a systematic review with comprehensive analysis of the published data. *Pain Med* 2014; 15: 386---402.
23. Cohen SP, Bicket MC, Jamison D, Wilkinson I, Rathmell JP. Epidural steroids: a comprehensive, evidence---based review. *Reg Anesth Pain Med*. 2013 May---Jun;38(3):175---200.
24. Carragee EJ, Han MY, Suen PW, Kim D. Clinical outcomes after lumbar discectomy for sciatica: The effects of fragment type and anular competence. *J Bone Joint Surg Am* 2003;85(1):102---8.
25. Dewing CB, Provencher MT, Riffenburgh RH, Kerr S, Manos RE. The outcomes of lumbar microdiscectomy in a young, active population: Correlation by herniation type and level. *Spine (Phila Pa 1976)* 2008;33(1):33---8.
26. Folman Y, Shabat S, Catz A, Gepstein R. Late results of surgery for herniated lumbar disk as related to duration of preoperative symptoms and type of herniation. *Surg Neurol* 2008;70(4):398---401.
27. Mysliwiec LW, Cholewicki J, Winkelpleck MD, Eis GP. MSU classification for herniated lumbar discs on MRI: Toward developing objective criteria for surgical selection. *Eur Spine J* 2010;19(7):1087---93.
28. Eriksen J, Sjogren P, Bruera E, Ekholm O, Rasmussen NK. Critical issues on opioids in chronic non---cancer pain: An epidemiological study. *Pain* 2006;125:172---9.
29. Sacerdote P, Manfredi B, Mantegazza P, Panerai AE. Antinociceptive and immunosuppressive effects opiate drugs: A structure---related activity study. *Br J Pharmacol* 1997;121:834---40.
30. Vallejo R, deLeon---Casasola O, Benyamin R. Opioid therapy and immunosuppression. A review. *Am J Ther* 2004;11:354---65.
31. Rajagopal A, Vassilopoulou---Sellin R, Palmer JL, Kaur G, Bruera E. Symptomatic hypogonadism in male survivors of cancer with chronic exposure to morphine. *Cancer* 2004;100:851---8.
32. Mao J. Opioid---induced abnormal pain sensitivity: Implications in clinical opioid therapy. *Pain* 2002;100:213---7.
33. Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in drug and opioid overdose deaths --- United States, 2000---2014. *MMWR Morb Mortal Wkly Rep*. 2016 Jan 1;64:1378---82.
34. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med*. 1999 Jun 17;340(24):1888---99.