Pain Management Injection Therapies for Low Back Pain
Project ID: ESIB0813, March 20, 2015
Disposition of Peer and Public Comments

Commenter	Section	Comment	Response
Peer Reviewers			
Reviewer 1	Introduction	OK	Noted.
Reviewer 1	Methods	OK, but many studies are missing. 2 SI joint studies in spondylarthropathy: Maugars et al. and a 2nd Luukkainen et al.	As described in the PICOTS, studies of patients with spondyloarthropathy were excluded. The Luukainen and Maugars trials both evaluated sacroiliac injections for spondyloarthropathy.
Reviewer 1	Results	I just attended (and spoke) at the FDA meeting on epidural steroid injections. There was nearly universal agreement that ESI were better than non-ESI through 6 weeks, which is different than this analysis. I spoke on effectiveness and showed a meta-analysis with 8 of the top studies (Tafazal, Karppinen, Cohen, Ghahreman etc.) that showed a 15% improvement at 4 weeks and a 10% at 6 weeks compared to the control (most of the time an epidural local anesthetic injection). Dr. John Farrar was there who did all of the research on "clinically meaningful benefit", serving on the panel. Basically, the difference compared to baseline in the ESI group was > 30%. The difference between the ESI and control group was > 10% through 6 weeks, which is more than the improvement for nearly all drugs used for neuropathic pain compared to placebo (pregabalin, gabapentin, duloxetine).	We reviewed the materials from the FDA session (http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm425962.htm). The analysis described was based on a selected set of studies and was not systematic; we reviewed the references and found none that met inclusion criteria. We also found epidural steroid injections associated with a small improvement in pain at up to 4 weeks, so we do not think there is an inconsistency there. As described in the report, there were no differences between epidural steroid injections vs. placebo interventions in the proportion of patients experiencing a successful outcome as defined by the trials (most commonly >50% improvement in pain). We added a reference to the FDA materials to the Discussion.
Reviewer 1	Results	In table A, the studies describing the findings should be referenced.	Thank you for your comment. We followed the AHRQ Procedure Manual for the format of this table. The studies are referenced in the text and in the tables and are cited in the relevant sections of the results.
Reviewer 1	Discussion / Conclusion	The limitations are discussed. The implications are not always clear	Noted. The purpose of the review is to summarize the evidence, not to make clinical or policy recommendations.
Reviewer 1	Clarity / Usability	Yes	Noted, thank you.
Reviewer 2	General Comments	The clinical utility of the report is inconclusive given the lack of high quality trials and the inherent difficulties (if not impossibility) of performing high quality trials for invasive procedures. Challenges include patient recruitment, lack of funding, and blinding. This stresses the importance of searching for alternative methods to study such as large scale multi center registries. Nonetheless, the authors did their very best in trying to answer the question on efficacy. The findings are not surprising.	Thank you for your comment. Over 50 trials of injections exist, suggesting that the ability to conduct trials is not a major barrier in this field.
Reviewer 2	Introduction	Introduction is adequate and states the problem and goal.	Noted, thank you.
Reviewer 2	Methods	Methods are appropriate and the group has a long track record of performing evidence based reviews.	Noted, thank you.

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Reviewer 2	Results	Adequate	Noted, thank you.
Reviewer 2	Discussion / Conclusion	The only thing I would add is a further discussion on the challenges of performing high quality research for invasive procedures as I describe above. Decades of attempts to perform high quality clinical trials in the area have failed. New approaches are needed. Clinical experience is not always consistent with the findings of such evidence based reviews. I think the authors do a good job in detailing the limitations of the review.	Thank you for your comment. Over 50 trials of injections exist, including higher-quality trials, so we do not necessarily agree that difficulty of conducting trials is the issue.
Reviewer 2	Clarity / Usability	As discussed above, I am concerned over using these findings by policy makers to trump clinical experience. As stated above, perhaps registries would be a better method to reach conclusions on efficacy.	Thank you for your comment. The purpose of the review is to summarize the evidence, not to make policy recommendations. Over 50 trials of injections exist; we do not believe that observational data such as that taken from registries should trump evidence from well-conducted clinical trials. Well-conducted RCTs may be particularly important for evaluating effects on subjective outcomes such as pain, which is more susceptible to placebo effects.
Reviewer 3	General Comments	Obviously a lot of time and effort went into this report led by Roger Chou who is a wonderful Guideline/Evidence expert. This report is very dense and will have tremendous policy implications that will affect the care our patients receive. The quality of evidence is uniformly low or absent yet conclusions reflect this only in implying that ESIs for example should not be used in patients with spinal stenosis. This is a conclusion that is not evidence based. Evidence based means using the best clinical evidence to help make a clinical decision. The absence of evidence does not mean treatment should not be offered. This report should emphasize with greater vigor and unequivocally state that the quality of evidence is low and that statements made in conclusions reflect the opinions of the authors and not the medical evidence. It should also state unequivocally that "policy regarding reimbursement for ESI should not be altered based on low quality evidence".	Thank you for your comment. The purpose of the review is to summarize the evidence, not to make clinical or policy recommendations.
Reviewer 3	General Comments	Your own definition of low is: A “low” grade indicates low confidence that the evidence reflects the true effect and further research is likely to change the confidence in the estimate of effect and is likely to change the estimate. This is buried in the report and when the only evidence is low, the conclusions reflect the bias of the authors. The authors should be very careful, and I know Roger is, not to harm patients based on low quality evidence.	Thank you for your comment. The definitions of the grades and grading system come from the AHRQ Methods Guide for Comparative Effectiveness Reviews. Low grades are based on shortcomings in quality, consistency, precision, directness, or other factors; conclusions are based on the (low-quality) evidence available and do not reflect biases of the authors. The purpose of the review is to summarize the evidence, not to make clinical or policy recommendations.

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Reviewer 3	General Comments	This report is not not clinically meaningful. It is confusing. Key questions are okay but authors need to ask themselves What can I convey that might be useful to readers? How can I convey it in a straightforward and clear manner that will not be subject to misinterpretation. I know Roger asks these questions but it is my feeling that the authors have not succeeded.	Thank you for your comment. The report follows the structure required by the AHRQ Methods Guide for Comparative Effectiveness Review. Key questions were developed with the input of CMS staff, Key Informants and the public.
Reviewer 3	Introduction	Okay	Noted.
Reviewer 3	Methods	All up to Rogers usual high standards.	Noted, thank you.
Reviewer 3	Results	Too much detail in text	Noted.
Reviewer 3	Discussion / Conclusion	Are the implications of the major findings clearly stated? No. This report will have resounding implications in the treatment available to my patients and my interpretation is that these procedures, eg ESI will be severely limited by payers based on low quality evidence.	The purpose of the review is to summarize the evidence, not to make clinical or policy recommendations.
Reviewer 3	Clarity / Usability	As stated, the report is quite dense, complex, and confusing. It is difficult to keep track of the authors intent sentence to sentence.	We attempted to make the report as usable and reader-friendly as possible. However, given the complexity of the material and the large volume of evidence, we acknowledge that it is a challenge. We believe the executive summary and summary tables and bullets provide usable summary information.
Reviewer 4	General Comments	The authors are to be congratulated on organizing and reporting a massive quantity of data on controlled trials describing response to spinal injection therapies in patients with “low back pain.” I will offer specific comments regarding areas of concern in each section of the document, but I wish to initially describe my discomfiture with the methodology utilized in this technology assessment. Although AHRQ has defined its methodology with rigor, and adheres to it in this study, this approach obscures important conclusions that emerge when the literature is reviewed more broadly. This takes on societal significance given that public policy will likely flow from this technology assessment. The opportunity for societal harms is not to be ignored.	Thank you for your comment. We reply to your specific comments as they are outlined below.

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Reviewer 4	General Comments	A primary conclusion of this study is that epidural steroid injections are associated with immediate improvements in pain and possible immediate improvements in function, but that the benefits are small and not sustained. I wish to examine this conclusion in reference to the methodology by which it was obtained. This commentary applies to the several questions posed in the AHRQ technology assessment, but is best illustrated by Question 1, addressing epidural steroid efficacy. The efficacy of injection therapies for radicular pain has been the subject of a great deal of research effort that is unexamined in this assessment. The inclusion criteria select for research methodology: randomized controlled trials of injection therapies versus placebo, randomized comparative effectiveness trials, and large observational trials only with respect to harms. The exclusion of high quality observational studies of clinical effectiveness removes important information and context from a synthesis of the literature. The legacy of Dr. Cochrane is the examination of efficacy, clinical effectiveness and efficiency, not efficacy alone. (1)	Thank you for your comment. While observational studies can be useful for harms and in certain instances, as is discussed in the AHRQ Methods Guide, they are highly susceptible to confounding and bias have been shown to be misleading in the field of low back pain as well as in many other fields of medicine, particularly when evaluating the effectiveness of interventions based on subjective outcomes. Therefore, well-conducted randomized trials remain the standard for evaluating the effectiveness of interventions. We do not agree that observational studies should take precedence over higher-quality randomized trials. In addition, over 50 trials of injections exist; therefore, we do not agree that trials are lacking in this area. Please also note that a Topic Refinement Document with Key Questions and PICOTS (including restriction to RCTs) was posted for public comment.

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Reviewer 4	General Comments	The emphasis on research methodology as the primary inclusion criteria may lead to an under-appreciation of other important characteristics of the studies under examination. Primary among them is specific diagnosis. Many of the studies in the analysis fail to adequately specify the process under treatment. There is no physiologic process beyond systemic effect by which steroids delivered to the epidural space would be expected to affect axial back pain arising from nociception in the intervertebral disc, facet joints, sacroiliac joint 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. (2) Many of the included studies have treated an undefined mix of axial and radicular pain patients; heterogeneity of response is expected, not surprising. The specificity of the diagnosis in the study populations was not included in the assessment of study quality. A randomized controlled trial (RCT) without careful patient selection is of no clinical value and may be misleading, yet its RCT methodology tends to purchase it credence. Examining the 29 studies of "epidural steroid injection" versus placebo, radicular pain alone was specified in 22, a mixture of radicular and back pain in 6 and back pain alone in one. A correlative imaging finding was required for inclusion in only 11 of 29 studies. The nature of the lesions being treated is thus largely unknown, and the degree of neural compression is completely unknown. Two studies have shown that the degree of neural compression is a predictor of success in transforaminal epidural steroid injections (TFESI). (3,4) With minimal neural compression the proportion of responders may be as high as 75%; with high grade compression the response rate may be as low as 25%. The lack of diagnostic specificity in patient selection is unfortunately emphasized by the lack of clarity in the title of this technology assessment. Here "low back pain" is deemed inclusive of axial pain, radicular pain without radiculopathy, and true radiculopathy with a neurologic deficit. The definitions used by the authors are at variance with accepted medical terminology in the fields of neurology and pain management. (5)	Thank you for your comment. We describe the patient populations and their diagnoses as it is reported in the studies. Key question 2 addresses how patient and other characteristics impact responsiveness to injections; as described, there was insufficient evidence to determine whether the cause of radicular symptoms, duration of symptoms, imaging findings, or other patient factors, or no clear association.

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Reviewer 4	General Comments	The techniques utilized in the administration of epidural steroids are also critical. No randomized studies examined the use of image guidance as a variable. This has, however, been well examined in non- randomized studies, which have shown that up to 74% of "epidural" steroid injections performed without image guidance either deposit medication external to the epidural space or do not reach the targeted pathology within the ventral epidural space. (6,7,8,9). Examining the 29 studies used to assess efficacy of epidural steroid injections versus a placebo, there were 15 interlaminar or presumed interlaminar epidural steroid injection (ILESI) studies of which only 1 used fluoroscopic guidance. There were 9 caudal injection studies of which only 1 reported fluoroscopic guidance. Five transforaminal epidural steroid injection (TFESI) studies all utilized fluoroscopic guidance. Hence, with the exception of the 5 TFESI trials, the studies of "epidural steroid injections" deposited an anti-inflammatory agent into an unknown tissue space that was unlikely to reach the site of inflammation.	Thank you for your comment. We examined the route of administration, including head-to-head trials, and stratified analyses (all main analyses are stratified by treatment approach); there were no patterns suggesting that the route of epidural steroid administration impacted results.
Reviewer 4	General Comments	While image guidance is essential, the technique of delivery is equally important. The ILESI and caudal injection studies suffer from the lack of image guidance, but also the lack of target specificity inherent in the techniques. Even when performed with image guidance these procedures 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. TFESI procedures place the needle in direct proximity to the target nerve and can verify delivery to that site by observing contrast media flow. It is not reasonable to combine TFESI procedures with ILESI or caudal injections in an evaluation of "epidural steroid injections."	Thank you for your comment. Although transforaminal injection may provide more targeted delivery of steroid, as described above we found no effects of route of administration on results.
Reviewer 4	General Comments	As a corollary, many of the included studies are 20-30 years old. Although the studies may be inappropriately aggregated as "epidural steroid injections," technology and clinical practice have not remained static. Surely the authors would not consider a study on coronary artery bypass grafting from the 1980's to be reflective of current surgical technique, and useful in evaluating expected outcomes in 2014.	We performed an analysis stratified by year of publication and found no effect on conclusions.

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Reviewer 4	General Comments	In addition to image guidance and injection technique, another neglected study characteristic is the method of reporting outcomes data. Many studies included in this analysis report only continuous data as a comparison between group means in reference to a minimum clinically important difference. Pain and functional disability data are not normally distributed. Rather, responses are often bimodal, with segregation into responder and non-responder populations that will be concealed by evaluating group means. Categorical outcomes that define the proportion of patients reaching a predefined responder status are critical to meaningful interpretation. (10) The authors recognize this, and included categorical outcomes when available, but such data often cannot be extracted from the manuscripts, leaving less useful continuous data. In the 5 trials comparing TFESI and ILESI, only continuous data was analyzed.	Thank you for your comment. As presented in the results, analyses on both continuous and dichotomous outcomes were presented. If anything, results using dichotomous outcomes (likelihood of experiencing a clinically meaningful benefit) showed less evidence of effectiveness than analyses based on continuous outcomes (mean change in pain or function scores).
Reviewer 4	General Comments	As ILESI and TFESI techniques are quite different in the likelihood of target specific corticosteroid delivery, it is essential to consider whether there are differences in outcomes. This study makes that assessment based on 5 randomized comparative effectiveness studies, and using pooled continuous data concludes there were no differences in pain relief or functional recovery at immediate or short term, and no difference in pain relief at intermediate term when 2 trials (11,12) “that used lower doses of corticosteroids for interlaminar than transforaminal injections were excluded.” This statement is false; both trials cited used the same dose of steroid for each procedure. Rather, the Rados trial (13), which is incorrectly cited (reference 94, not 142, in the AHRQ assessment), is included in the weighted means despite using twice the steroid dose for interlaminar injections than transforaminal injections. Looking at the studies individually, a study of TFESI versus ILESI versus Caudal injections in patients with radicular pain and correlative imaging (11), using the same steroid doses, showed significantly greater proportions of TFESI patients achieving a categorical outcome for pain relief, with significantly lower levels of pain at 24 weeks, than ILESI or caudal injections. TFESI delivered the medication to the ventral epidural space at the target segment significantly more often, which correlated with pain outcomes. Another study (14) showed significantly greater improvements in pain relief and functional recovery at 6 months for TFESI vs ILESI. One study (15) showed significantly greater improvements in pain relief with TFESI vs ILESI, but with measurement only at 10-16 days. Another study compared	Thank you for your comment. There was a typo in the report, it should have said, "that used lower doses of corticosteroid for transforaminal than interlaminar injections." The two trials were Gharibo and Rados; we corrected the error (there were no differences in stratified analyses according to whether the trials used equivalent doses or lower doses with transforaminal versus interlaminar injection." We also performed an analysis in which a trial (Kolsi) that evaluated a "nerve root injection" (in which it was unclear if injectate entered the epidural space) was excluded, and there was also no difference. Pooled results at immediate-term, short-term, and intermediate-term are reported; none showed a difference between IL vs. TF epidural steroid injections. We corrected the Rados reference (mistakenly cited Rados 2013 instead of Rados 2011).

Commenter	Section	Comment	Response
		similar steroid doses, but performed periradicular, not epidural injections; it is unknown if this provided distribution to the ventral epidural space, which is necessary for efficacy (16).	
Reviewer 4	General Comments	Failure to closely evaluate the details of procedural performance in RCTs may result in inappropriate inclusion in pooled data. The utility of pooled group means is itself unclear. The available categorical data suggests the TFESI approach is superior to ILESI. Another method of examination of the efficacy of TFESI versus other epidural injections is comparison of outcomes from explanatory trials. Data from explanatory trials of non-image guided injections yields a number needed to treat > 90. (17, 18, 19, 20, 21) In contrast, a high quality explanatory trial of TFESI yields a number needed to treat of 3. (22) These are distinct procedures that must be evaluated separately. The inclusion of ILESI and caudal injections with TFESI in an artificial category of "epidural steroid injections" is not reasonable.	As stated above, all main analyses were stratified by the approach used and we performed additional analyses on head-to-head trials comparing difference epidural steroid injection approaches. As described in the report, we found no evidence of differences in effectiveness between techniques.
Reviewer 4	General Comments	The methodological flaw of relying only on RCT evidence, and creating an artificial category of "epidural steroid injections", is brought into focus by examining a broader synthesis of the data supporting TFESI. The most rigorous controlled trial supporting the efficacy of TFESI in patients with radicular pain due to disc herniations compared transforaminal steroids with 4 control arms using categorical outcomes of ≥ 50% pain relief at one month. (22) Note that this trial required a correlative lesion on imaging; it is incorrectly stated in the AHRQ assessment that it did not do so. Transforaminal injection of steroid produced 54% (95% CI 36, 72) responders, significantly greater than the control arms, which were indistinguishable from one another (15% responders, 95% CI 8, 22). All patients who were relieved of their pain were restored to normal or near normal function, and reduced their need for other health care. All patients previously requiring opioids ceased opioids. These significant outcomes were concealed by continuous data (group means). Another controlled trial used surgical sparing as the primary outcome. Only 29% of patients required surgery after treatment with transforaminal steroids injections compared with 67% treated with transforaminal local anesthetic. (23) The effects were durable in a five-year follow-up study of these patients. (24) A recent supportive observational trial studied patients awaiting surgery for radicular pain; 56% (CI 46, 66) avoiding surgery after a successful TFESI. (25) A randomized, controlled comparative effectiveness trial of TFESI with two steroid formulations showed that 70% of patients with radicular pain due to disc herniation had ≥ 50% pain relief that was durable at 6 months. (26) Clinical	Thank you for your comment. As noted previously, observational studies on effectiveness were excluded. The RCTs described by the commenter were included in the report. Reference 22 (Ghahreman) in the draft was rated fair-quality, as the persons performing injections were blinded to whether steroid, local anesthetic, or saline was administered transforaminally, but not to use of the other control interventions (intramuscular saline or steroid). We analyzed both dichotomous and continuous outcomes from this trial. Reference 23 (Riew) was also included; it had a number of methodological limitations (including high attrition at 5 year follow-up) and was rated fair-quality; it is included in the analyses that looked at surgery as an outcome. Reference 26 (Kennedy) was included in the section comparing injections with two different steroids; there was no placebo intervention in this trial. As described above, key question 2 addresses effects of patient characteristics on effectiveness of epidural steroid injections, including duration of pain. The results reported by the commenter from the cited systematic review do not represent results of epidural steroid injections versus placebo interventions but are uncontrolled (before-after) results in patients receiving injections that are not interpretable because of the lack of a control group comparison.

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		effectiveness was further supported by a large observation study of prospectively collected data on > 2000 consecutive patients receiving a single TFESI for radicular pain due to disc herniation, fixed lateral recess or foraminal stenosis. (27) In this study 46% were responders for pain relief (95% CI 43, 49) and 41% (38, 44) for functional recovery. When patients were segregated by duration of pain syndrome, those with sub-acute pain (< 3 months duration) had 62% (CI 56, 68) responders for pain relief and 59% (CI 53,65) responders for functional recovery, significantly better than patients with chronic pain. This important information cannot be derived from the small RCTs included in the AHRQ assessment. The important clinical question of the effectiveness of repeat epidural steroid injections is not addressed by a study with methodology qualifying for inclusion in the assessment. However, a recent observational study of prospectively acquired data on over 2000 TFESI in 933 patients demonstrated that repeat TFESI are less effective than an index intervention, although not by a clinically relevant amount. More responsive sub-acute pain patients recovered all prior benefit in pain relief from an index injection that had since waned; early repeat injections for incomplete responders provided cumulative benefit. (28) A systematic review synthesized all the evidence from 6 explanatory trials, 11 pragmatic trials and 20 observational studies of lumbar TFESI and concluded that up to 70% of patients with radicular pain due to disc herniations achieve 50% pain relief at 1-2 months after treatment and 30% achieve complete relief. Between 25% and 40% of patients have relief that lasts 12 months. (29)	
Reviewer 4	General Comments	The methodology of the AHRQ health technology assessment, with its exclusive reliance on controlled trials, some of them up to 30 years old, which do not carefully consider specific diagnosis (patient selection), standardized technical performance of procedures, or the use of categorical outcomes data, limits the clinical usefulness of this assessment in my judgment. I applaud the heroic effort to assemble this data, but believe it paints an incomplete and misleading view of the totality of the literature. The application of this methodology to Question 1 fails to identify the well-established efficacy and clinical effectiveness of TFESI for radicular pain due to disc herniations from the larger pool of inappropriately aggregated studies of "epidural steroid injections." Formulation of public policy on this basis is flawed.	Thank you for your comment. While observational studies can be useful for harms and in certain instances, as is discussed in the AHRQ Methods Guide, they are highly susceptible to confounding and bias have been shown to be misleading in the field of low back pain as well as in many other fields of medicine, particularly when evaluating the effectiveness of interventions. Therefore, we do not agree that observational studies should take precedence over higher-quality randomized trials. In addition, over 50 trials of injections exist; therefore, we do not agree that trials are lacking in this area. Please also note that a Topic Refinement Document with Key Questions and PICOTS (including restriction to RCTs) was posted for public comment. The purpose of this report is to synthesize the evidence, not to make clinical or public policy recommendations.

Commenter	Section	Comment	Response
Reviewer 4	General Comments	References: 1. Haynes, B. Can it work? Does it work? Is it worth it? BMJ 1999;319:652. 2. 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. 3. Ghahreman A, Bogduk N. Predictors of a favorable response to transforaminal injection of steroids in patients with lumbar radicular pain due to disc herniation. Pain Med 2011;12(6):871–9. 4. Choi SJ, Song JS, Kim C, et al. The use of magnetic resonance imaging to predict the clinical outcome of non-surgical treatment for lumbar intervertebral disc herniation. Korean J Radiol 2007;8:156–63. 5. Merskey H, Bogduk N (eds). Classification of Chronic Pain. Descriptions of Chronic Pain Syndromes and Definition of Pain Terms, 2nd edn. IASP Press, Seattle, 1994. 6. Fredman B, Nun MB, Zohar E, Iraqi G, Shapiro M, Gepstein R, Jedeikin R. 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Riew KD, Yin Y, Gilula L, Bridwell KH, Lenke LG, Lauryssen C, Goette K. 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 Nov;82-A(11):1589-93. 24. Riew KD, Park JB, Cho YS, et al. Nerve root blocks in the treatment of lumbar radicular pain.	Thank you for providing references. We reviewed them for inclusion in the report. All of the studies were either already included or did not meet inclusion criteria, with the exception of Ghahreman 2011 (additional results from a previously included trial), which has been added.

Commenter	Section	Comment	Response
		A minimum five-year followup. J Bone Joint Surg Am. 2006 Aug;88(8):1722-5. 25. Manson NA, McKeon MD, Abraham EP. Transforaminal epidural steroid injections prevent the need for surgery in patients with sciatica secondary to lumbar disc herniation: a retrospective case series. Can J Surg 2013; 56 (2): 89-96. 26. Kennedy DJ, Plastaras C, Casey E, Visco CJ, Rittenberg JD, Conrad B, Sigler J, Dreyfuss P. 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; 15 (4): 548-55. 27. Kaufmann TJ, Geske JR, Murthy NS, Thielen KR, Morris JM, Wald JT, Diehn FE, Amrami KK, Carter RE, Shelerud RA, Gay RE, Maus TP. Clinical effectiveness of single lumbar transforaminal epidural steroid injections. Pain Med 2013; 14 (8): 1126-33. 28. Murthy NS, Geske JR, Shelerud RA, Wald JT, Diehn FE, Thielen KR, Kaufmann TJ, Morris JM, Lehman VT, Amrami KK, Carter RE, Maus TP. The effectiveness of repeat lumbar transforaminal epidural steroid injections. Pain Med 2014; 15 (10): 1686-94. 29. 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 (1): 14-28.	
Reviewer 4	Introduction	The introduction suggests that injection therapies for “low back pain” are directed toward a nonspecific and un-diagnosable process. This is an assertion not based on contemporary evidence. If the authors wish to make this argument, contemporary primary evidence should be cited, if it exists, not their own 12 year-old review article. (ES-1, line 39) The authors should acknowledge that recent literature describes that the systematic application of diagnostic injection procedures can identify specific pain generators (1,2,3) that may then be targeted by specific therapeutic procedures. It is a questionable intellectual leap to conduct a health technology assessment of therapeutic procedures directed toward a symptom, “low back pain,” without a robust discussion of the diagnosis of specific pathophysiologic processes that may be manifest as this symptom.	We replaced the reference with a recent manuscript on low back imaging from the American College of Physicians. Guidelines from the American College of Physicians and others state that most low back pain cannot be reliably attributed to a specific source of low back pain. Because of the lack of a reference standard for specific causes of non-radicular low back pain, the accuracy of diagnostic injections procedures for diagnosis of specific sources of low back pain is unknown. Our report includes evidence on how use of diagnostic procedures impacts effectiveness; there is no evidence that use of diagnostic injection procedures improves effectiveness.

Commenter	Section	Comment	Response
Reviewer 4	Introduction	The definition provided of the symptom, “low back pain” highlights the false premise on which the assessment is based. In the Scope of Review and Key Questions illustration, “Nonspecific, subacute or chronic low back pain” are said to be inclusive of “non-radicular low back pain, low back pain with radiculopathy and low back pain with spinal stenosis.” There is an implicit contradiction here in that there are specific criteria for the diagnosis of axial pain and radiculopathy. Radiculopathy is correctly defined as requiring specific evidence of neural dysfunction on physical exam, to include objective weakness, objective anesthesia, or diminished deep tendon reflexes, or electro-physiologic evidence of neural dysfunction- it is objective, not non-specific. (4) Radicular pain without radiculopathy can be diagnosed by selective nerve blocks. (5) Spinal stenosis is an imaging observation. It is not a disease process. If the authors wish to refer to the recognized disease process of neurogenic intermittent claudication, perhaps best defined in the guidelines of the North American Spine Society, they should do so specifically. (6) Somatic axial pain experienced in the lumbar region can be specifically attributed to the facet joints (dual comparative medial branch blocks), the intervertebral disc (disc stimulation), or the sacroiliac joint (controlled intra-articular blocks and multi-site, multi-depth lateral branch blocks). (5) It is unfortunate that this health technology assessment does not begin by careful definition of the pathophysiologic processes to be treated by the technology to be assessed. The aggregation of somatic axial lumbar pain, radicular pain with or without radiculopathy, and neurogenic intermittent claudication into the symptom complex “low back pain” sets the stage for confusion and uncertainty. This is analogous to a health technology assessment of therapy for the symptom of chest pain, inclusive of bacterial pneumonia, acute coronary syndrome, and pulmonary embolism. The technology assessment loses credibility at its inception by failing to clearly identify the disease process being treated and the means of its diagnosis.	Guidelines from the American College of Physicians and others state that most low back pain cannot be reliably attributed to a specific source of low back pain. Because of the lack of a reference standard for specific causes of non-radicular low back pain, their accuracy is unknown. Our report includes evidence on how use of diagnostic procedures impacts effectiveness; there is no evidence that use of diagnostic injection procedures improves effectiveness. As described in other responses to this commenter, the report evaluates how patient characteristics (such as use of imaging to select patient, use of diagnostic injection techniques, or specific clinical criteria).
Reviewer 4	Introduction	The authors are inclusive of ablative therapies in the definition of the injection therapies which the topic of this technology assessment, and then exclude them paragraphs later. Perhaps the definition of the boundaries of the technology assessment could be made from the outset. (ES-1, Line 53)	We revised to clarify that ablative therapies are other "interventional" therapies but do not involve the injection of medications into the spine.

Commenter	Section	Comment	Response
Reviewer 4	Introduction	The authors appropriately point out that the use of spinal therapeutic injections dramatically increased in the late 1990s and the early 2000s. More recent data, presented at the US Food and Drug Association Advisory Panel meeting on epidural steroid injections in Silver Spring, MD (Nov 24, 25, 2014), showed only a modest increase in the absolute number of epidural injections performed from 2009-2013. Annual numbers of epidural steroid injections in Medicare patients (> 65 years of age) increased by 20.5%, while commercially insured epidural steroid injections in the same age group increased by 19.8%. (7) In this time period (2009-2013) the US population > 65 years of age increased by 13.0%. (8) The recent increase in the rate of epidural steroid usage in this age group is decidedly modest. Contemporary data would be appropriate in this health technology assessment, as it is available from other agencies of the federal government.	The data is accurate as presented, noting a 187% growth between 2000 and 2008. The data regarding trends from 2009 to 2013 are from an FDA document and has not been published in the peer reviewed literature; therefore, we think it is premature to include it at this time.
Reviewer 4	Introduction	The authors correctly identify many of the reasons for the heterogeneity in the results of studies of the various injection therapies, including definition of terminology, patient selection, varied injection technique, and insufficient duration of follow up. This acknowledgement only makes more puzzling the use of non-standard definitions of terminology, the aggregation of multiple pathophysiologic processes into an ill-defined symptom complex, and the aggregation of techniques (interlaminar, caudal, transforaminal, and periradicular injections grouped into a heterogeneous category of epidural steroid injections). The variations in patient selection are acknowledged, but there is insufficient stratification of studies by rigorous patient selection or injection technique.	As noted earlier, all analyses were stratified by the injection technique used and head-to-head trials were separately analyzed; there was no evidence of any differences in effects. In addition, key question 2 addresses effects of patient characteristics such as presenting symptoms and methods of selection, again findings no effects. Trials of injections for radicular back pain, non-radicular back pain, spinal stenosis, sacroiliac pain, and post-surgical pain were evaluated separately.
Reviewer 4	Introduction	Note that the definition of transforaminal injections “through the neuroforamen dorsal to the exiting nerve root” is not strictly correct. In the most commonly performed supraneural transforaminal approach the needle is directly superior to the exiting nerve, not dorsal to it. In other variations of the transforaminal approach, the retroneural or infraneural approaches, the needle will lie dorsal to the exiting nerve. Throughout the document, it is apparent that the authors have no specific knowledge of the procedures they critique. This is unfortunate; inclusion of experts in the field to better shape the methodology of inquiry would have likely yielded a more useful assessment. As Dr. Sackett noted in his commentary on evidence based medicine: “Without clinical expertise, practice risks becoming tyrannised by evidence, for even excellent external evidence may be inapplicable to or inappropriate for an	Thank you for the comment. Technical experts reviewed the protocol, which included the description of transforaminal injections, and a Topic Refinement Document with Key Questions and PICOTS was posted for public comment. There are a number of transforaminal procedures. We revised to state more non-specifically "through the neuroforamen of the exiting nerve root."

Commenter	Section	Comment	Response
		individual patient."(9)	
Reviewer 4	Introduction	The formulation of the key questions suffers from the attempt to generalize across application of a heterogeneous group of procedures to an inadequately defined symptom complex. Many of the more rational specific questions are subsequently developed in the data presentation.	As noted previously, key question 2 evaluated the effects of patient characteristics, including patient symptoms, on the effectiveness of injections. In addition, analyses were performed separately for injections for radicular symptoms, non-radicular symptoms, spinal stenosis, and post-surgical pain syndromes.
Reviewer 4	Introduction	References: 1. DePalma MJ, Ketchum JM, Saullo T. What is the source of chronic low back pain and does age play a role? Pain Med 2011; 12 (2): 224-33. 2. DePalma M, Ketchum J, Saullo T, Schofferman J. Structural etiology of chronic low back pain due to motor vehicle collision. Pain Med 2011; 12 (11): 1622-7. 3. DePalma MJ, Ketchum JM, Saullo TR. Multivariable analyses of the relationships between age, gender, and body mass index and the source of chronic low back pain. Pain Med 2012; 13 (4): 498-506. 4. Merskey H, Bogduk N (eds). Classification of Chronic Pain. Descriptions of Chronic Pain Syndromes and Definition of Pain Terms, 2nd edn. IASP Press, Seattle, 1994. 5. Bogduk N ed. Practice guidelines for spinal diagnostic and treatment procedures. 2nd edition. International Spine Intervention Society. San Francisco, USA 2013. 6. North American Spine Society. Evidence-based clinical guidelines for multidisciplinary spine care, diagnosis and treatment of degenerative lumbar spinal stenosis. Burr Ridge (IL): North American Spine Society; 2011. 7. US Food and Drug Administration. http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm425962.htm 8. US Census Bureau. http://www.census.gov/popest/data/historical/index.html 9. Sackett DL, et al. Evidence based medicine: what it is and what it isn't. BMJ 1996 Jan 13;312:71-72.	Thank you for providing references. We reviewed them for inclusion in the report. None of the studies met inclusion criteria.
Reviewer 4	Methods	The problematic selection of studies for inclusion in this assessment based on research methodology, without due consideration for proper patient selection (diagnostic specificity), procedural technique, or use of categorical outcomes measures creates serious doubt as to the validity or utility of this health technology assessment. This is detailed in the general comments section of my review. I will make only more selective comments here.	Thank you for your comment. As noted previously, we do not believe that observational data such as that taken from registries should trump evidence from well-conducted clinical trials. Well-conducted RCTs may be particularly important for evaluating effects on subjective outcomes such as pain, which is more susceptible to placebo effects. We examined the factors mentioned and there were no patterns suggesting an effect on results or conclusions.

Commenter	Section	Comment	Response
Reviewer 4	Methods	The definition of “radiculopathy” (ES-4, line 30) is in conflict with that typically used in the fields of neurology or pain medicine. (1)	Our definition of radiculopathy ("presence of leg pain [typically worse than back pain]), with or without sensory deficits or weakness, in a nerve root distribution") is consistent with the definition used in the American College of Physicians/American Pain Society guideline (dysfunction of a nerve root associated with pain, sensory impairment, weakness, or diminished deep tendon reflexes in a nerve root distribution) and we believe is clinically relevant and appropriate for the purpose of this report.
Reviewer 4	Methods	The inclusion of “therapeutic medial branch blocks” is unexpected. Although addressed in one study, there is no acceptance of this procedure in the field of pain medicine. Dual, comparative medial branch blocks are the only validated, diagnostic procedure for facet mediated pain, but are specifically described as having no therapeutic value in contemporary practice guidelines. (2) There is no physiologic mechanism by which such a procedure could be expected to be effective.	The interventions were selected with the input of CMS, Key Informants, and the public. In addition, several trials of medial branch blocks assessed therapeutic effects, including in comparison with steroid injection. Therefore, we believe their inclusion was appropriate.
Reviewer 4	Methods	Assessing Quality (ES-6, 7): As noted in the General Comments discussion, the failure to include diagnostic specificity (patient selection) and technical performance of the procedures in the assessment of study quality dooms this process from its inception. It cannot be truthfully stated that this document represents an assessment of efficacy of the procedures said to be under study. It can be argued that it represents an assessment of the heterogeneity of efficacy outcomes of existing clinical practice over a period of 30 years, but those are very different things. Study Quality assessment is addressed in greater detail in the following section.	Thank you for your comment. Details on patient selection and technical performance of the procedures are reported. The studies were rated for quality (risk of bias) using standardized criteria, as described in the Methods. Trials were rated using criteria from the Cochrane Back Group (Furlan 2009 article published in Spine), in conjunction with the approach in the AHRQ Methods Guide. The characteristics that you describe are not factors related to risk of bias, but rather issues of external validity (e.g., selection of patients and techniques used) and as described earlier are addressed in detail.
Reviewer 4	Methods	In the description of categorical outcomes measures (ES-8, line 28) for function, the authors only refer to the Oswestry Disability Index; the Roland Morris Disability Questionnaire (RDQ) is also referenced earlier. The appropriate level for minimally significant improvement in the RDQ is 40%, not the 50% used for the ODI. (3)	The >50% improvement in the Oswestry Disability Index (ODI)for a dichotomous outcome was given as an example (and was the most commonly used definition for a clinically important outcome in the trials); the Results describe the different definitions used for a clinically important difference. As noted earlier in this paragraph, we pooled data for the ODI, Roland Morris Disability Questionnaire (RDQ), and other outcomes.
Reviewer 4	Methods	References 1. Merskey H, Bogduk N (eds). Classification of Chronic Pain. Descriptions of Chronic Pain Syndromes and Definition of Pain Terms, 2nd edn. IASP Press, Seattle, 1994. 2. Bogduk N ed. Practice guidelines for spinal diagnostic and treatment procedures. 2nd edition. International Spine Intervention Society. San Francisco, USA 2013. 3. Lauridsen HH, Hartvigsen J, Manniche C, Korsholm L, Grunnet-Nilsson N. Responsiveness and minimal clinically important difference for pain and disability instruments in low back pain patients. BMC Musculoskelet Disord 2006; 7: 82.	Thank you for providing references. We reviewed them for inclusion in the report. None of the studies met inclusion criteria.
Reviewer 4	Results	A comprehensive review of the study is found in the general comments section; the problematic inclusion and exclusion of studies are dealt with in that broader discussion of the technology assessment. I will limit my comments here to more selective issues.	Thank you for your comment. Please see specific comments for responses.

Commenter	Section	Comment	Response
Reviewer 4	Results	Study Quality Regarding the assessment of study quality, three studies (1,2,3) of epidural injections for “radiculopathy” were rated “good.” Two of those studies used only continuous data in outcomes measurements, and did not require a correlative neural compressive lesion on imaging. (2,3) One study (3) used topographical landmarks augmented by ultrasound to identify the sacral hiatus for caudal epidural injections. There was no use of fluoroscopy, hence it is completely unknown where the medication was delivered- in the epidural space, surrounding musculature, or intravascular. It is absurd to classify this as a ”good” study. This underscores the lack of technical awareness of procedural detail by the collective authorship. In contrast, the study widely regarded as the most elegant randomized controlled trial of TFESI (4), which required patients with radicular pain and a correlative lesion (incorrectly stated, page 73), and measured categorical outcomes for pain, as well as functional outcomes, surgical sparing, and other health care use, was rated as “fair.” Another randomized controlled trial compared TFESI to intramuscular saline injections, with a mean follow up of 1.4 years using a composite categorical outcome (> 50% reduction in pain and improvement in Roland –Morris score by > 5 points and a positive global effect score; all measured > 1 year post treatment). There were 84% responders in the TFESI group versus 48% for the control intervention. (5) This trial was excluded from evaluation for “wrong study design for key question.” (page 245, D-1) The exclusion of this study is not understandable.	Thank you for your comment. The studies were rated for quality (risk of bias) using standardized criteria, as described in the Methods. Trials were rated using criteria from the Cochrane Back Group (Furlan 2009 article published in Spine), in conjunction with the approach in the AHRQ Methods Guide. The characteristics that you describe are not factors related to risk of bias, but rather issues of external validity (e.g., selection of patients and techniques used) and as described earlier are addressed in detail. Although the Vad study (reference 5) describes itself as a randomized study, its methods state that patients were "randomized by patient choice"-- meaning that it was not randomized at all and therefore excluded.
Reviewer 4	Results	The single “good” comparative effectiveness study of epidural injections for ”spinal stenosis,” (presumably directed against the disease process of neurogenic intermittent claudication) was well conceived but suffered significant heterogeneity in patient selection, medication dose, and delivery technique. (6)	Thank you for your comment. The studies were rated for quality (risk of bias) using standardized criteria, as described in the Methods. Trials were rated using criteria from the Cochrane Back Group (Furlan 2009 article published in Spine), in conjunction with the approach in the AHRQ Methods Guide. The characteristics that you describe are not factors related to risk of bias, but rather issues of external validity (e.g., selection of patients and techniques used) and as described earlier are addressed in detail.

Commenter	Section	Comment	Response
Reviewer 4	Results	Among the several studies of facet injections, one study was rated "good." (7) This study used as its inclusion criteria for facet intervention "positive" MRI findings for facet hypertrophy and a positive response to an intra-articular local anesthetic injection. There is no evidence of any correlation between structural changes of facet hypertrophy and facet joint pain. (8) Intra-articular facet injections of anesthetic have never been validated as a diagnostic procedure and have an unknown placebo response rate. The only validated diagnostic procedure for facet-mediated pain is controlled medial branch block. (9) The criteria used to assess the quality of studies reflect research methodology, but fail to identify other procedural features that affect the validity of those studies. The categorization of studies makes clear that the authors are not familiar with the conduct of these procedures, nor the technical features that may affect efficacy or effectiveness. The study quality assessment is not credible.	Thank you for your comment. The studies were rated for quality (risk of bias) using standardized criteria, as described in the Methods. Trials were rated using criteria from the Cochrane Back Group (Furlan 2009 article published in Spine), in conjunction with the approach in the AHRQ Methods Guide. The characteristics that you describe are not factors related to risk of bias, but rather issues of external validity and as described earlier are addressed in detail.
Reviewer 4	Results	Synthesis As an example of how the exclusion of all but controlled studies leads to an incomplete and distorted view of the totality of the literature, consider the discussion on page 27 regarding comparative effectiveness studies of different corticosteroids in epidural injections. Only two studies are included (10,11); they constitute but a sample of several important studies examining the effectiveness of particulate versus non-particulate steroid preparations (suspensions versus solutions). All of the 13 case reports of spinal cord infarcts after lumbar TFESI occurred with particulate steroids. These are presumed to act as embolic agents following introduction into a radiculomedullary artery contributing to the anterior spinal artery. No catastrophic outcomes have occurred with the non-particulate steroid dexamethasone. Small comparative effectiveness studies had shown trends toward greater effectiveness of particulate steroids in cervical TFESI (12,13) The Park study (10) showed significantly greater improvement in one pain measure (VAS), but not another (McGill pain questionnaire, not mentioned in the AHRQ assessment) for particulate steroids. There was no difference between particulate and non-particulate steroids in functional improvement. Interventional pain physicians were left in a safety versus efficacy quandary: greater safety with dexamethasone, but possible diminished effectiveness. The Kennedy comparative effectiveness study (11) was significant. It utilized appropriate pain relief and functional recovery categorical outcomes measured at 6 months, and	Thank you for your comment. The Kennedy trial was included and discussed in the results. Over 50 trials of injections exist; we do not believe that observational data such as that taken from registries or case reports should trump evidence from well-conducted clinical trials. Well-conducted RCTs may be particularly important for evaluating effects on subjective outcomes such as pain, which is more susceptible to placebo effects. Large controlled observational studies of harms were included. Case reports of harms were not included because it is not possible to determine comparative risks from them. They are noted in the Discussion ("cases of serious neurological complications have been reported following lumbar epidural injections") and clinical and policy decision-makers may choose to consider them if they wish.

Commenter	Section	Comment	Response
		showed there was no difference in effectiveness of particulate versus non-particulate steroid formulations. This was reinforced by a large observational study of prospectively collected data on > 3,600 consecutive TFESIs with a non-inferiority analysis of the effectiveness of dexamethasone versus particulate steroids. (El-Yahchouchi, 14) Dexamethasone was non-inferior to the particulate steroids in pain and functional recovery categorical outcomes, despite higher glucocorticoid equivalents delivered in particulate steroid patients. Looking over the entirety of the literature, earlier studies (10,12,13) measured outcomes as 2-4 weeks, where there was a trend favoring the particulate steroids. This trend was also seen in the early data points of the Kennedy and El-Yahchouchi studies, but it completely fell away at 2 months post injection and beyond, where particulate and non-particulate steroids were indistinguishable in effectiveness. At intermediate term evaluation, there was no difference in effectiveness of particulate versus non-particulate steroids, and the safer non-particulate was therefore preferred. These latter studies (11, 14) form the basis of the soon to be published FDA Safe Use Initiative on epidural steroid injections. Evaluation of a small fragment of the literature drawn from a much larger clinical practice narrative thus is uninformative, and misleading.	
Reviewer 4	Results	The presentation of the tabular results is exhaustive. The authors are to be congratulated in the successful assemblage of all this information. Although tedious to deal with in PDF format, I have no suggestions for remediation.	Thank you for your comment.
Reviewer 4	Results	Based on the fundamentally flawed methodology, I am in strong disagreement with several of the presented results. Most importantly, it is my assessment that, in contrast to the inappropriately aggregated data regarding epidural steroid injections presented by AHRQ, the totality of the literature demonstrates, in clinical terms:	Thank you for your comment. The results of our evidence synthesis, using the methods outlined in the report, are presented in the Abstract, Executive Summary, Results (summarized in Key Points), Discussion, and Summary of Evidence Table.
Reviewer 4	Results	There is strong evidence for immediate, short and intermediate term categorical improvement in pain and functional deficit due to lumbar radicular pain with or without radiculopathy following technically well performed lumbar transforaminal epidural steroid injections. The evidence is strongest in patients with disc herniations as the cause of the radicular pain. There is evidence of modest quality for a surgical sparing effect for transforaminal epidural steroid injections.	Thank you for your comment. The results of our evidence synthesis, using the methods outlined in the report, are presented in the Abstract, Executive Summary, Results (summarized in Key Points), Discussion, and Summary of Evidence Table.

Commenter	Section	Comment	Response
Reviewer 4	Results	Transforaminal epidural steroid injections are superior to unguided interlaminar and caudal epidural steroid injections in immediate, short and intermediate term relief of radicular pain with or without radiculopathy and in functional recovery.	Thank you for your comment. The results of our evidence synthesis, using the methods outlined in the report, are presented in the Abstract, Executive Summary, Results (summarized in Key Points), Discussion, and Summary of Evidence Table.
Reviewer 4	Results	Particulate and non-particulate steroids are indistinguishable in clinical effectiveness (pain relief and functional recovery) in the immediate, short and intermediate term when delivered by transforaminal epidural injection as a treatment for radicular pain with or without radiculopathy.	Thank you for your comment. The results of our evidence synthesis, using the methods outlined in the report, are presented in the Abstract, Executive Summary, Results (summarized in Key Points), Discussion, and Summary of Evidence Table.
Reviewer 4	Results	Although I disagree with the methodology, I concur with these conclusions of the AHRQ technology assessment, rendered in clinical terms:	Thank you for your comment. Please see below for our specific responses.
Reviewer 4	Results	There is no evidence that unguided interlaminar or unguided caudal epidural injections provide benefit in pain relief or functional recovery from radicular pain with or without radiculopathy.	Noted.
Reviewer 4	Results	There is no evidence that epidural steroid injections by any technique provide benefit in pain relief or functional recovery for non-radicular pain.	Noted.
Reviewer 4	Results	There is insufficient evidence at this time to support epidural steroid injections as a therapy for neurogenic intermittent claudication. Better-controlled studies could alter this assessment.	Noted.
Reviewer 4	Results	There is insufficient evidence to assess epidural steroid injections versus other interventions. This could be done by comparison of categorical outcomes in placebo controlled trials, if such exist for the other interventions, in the absence of head to head trials. This is of critical importance, as competing technologies, including non-steroidal anti-inflammatory agents, opioids, and surgical intervention carry a known risk of harms.	Noted.
Reviewer 4	Results	There is no current evidence to support the diagnostic or therapeutic use of intra-articular facet injections. No studies have yet been published in which the study cohort has an established diagnosis of facet-mediated pain via controlled medial branch blocks. Until this is reported, the key question of therapeutic efficacy remains unaddressed.	Noted.
Reviewer 4	Results	There is no evidence to support the use of corticosteroids for a purported therapeutic medial branch block.	Noted.
Reviewer 4	Results	There is insufficient evidence to evaluate the efficacy or effectiveness of intra-articular sacroiliac joint injections.	Noted.
Reviewer 4	Results	There is a very low risk of harms associated with epidural steroid injections, or intra-articular facet injections.	Noted.

Commenter	Section	Comment	Response
Reviewer 4	Results	I have made no attempt to respond to the hundreds of results statements, but have focused on those I believe most relevant to patient care.	Thank you for your comment.
Reviewer 4	Results	On page 31, line 48, the wrong Cohen trial is cited. It should be reference 64.	Thank you, we corrected the reference.
Reviewer 4	Results	References 1. Cohen SP, White RL, Kurihara C, et al. Epidural steroids, etanercept, or saline in subacute sciatica: a multicenter, randomized trial. Ann Intern Med. 2012 Apr 17;156(8):551-9. PMID: 22508732. 2. Karppinen J, Malmivaara A, Kurunlahti M, et al. Periradicular infiltration for sciatica: a randomized controlled trial. Spine (Phila Pa 1976). 2001 May 1;26(9):1059-67. PMID: 11337625. 3. Iversen T, Solberg TK, Romner B, et al. Effect of caudal epidural steroid or saline injection in chronic lumbar radiculopathy: multicentre, blinded, randomised controlled trial. BMJ. 2011;343 4. 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. 5. Vad VB, Bhat AL, Lutz GE, Cammisa F. Transforaminal epidural steroid injections in lumbosacral radiculopathy: a prospective randomized study. Spine (Phila Pa 1976) 2002; 27 (1): 11-6. 6. Friedly JL, Comstock BA, Turner JA, Heagerty PJ, Deyo RA, Sullivan SD, Bauer Z, Bresnahan BW, Avins AL, Nedeljkovic SS, Nerenz DR, Standaert C, Kessler L, Akuthota V, Annaswamy T, Chen A, Diehn F, Firtch W, Gerges FJ, Gilligan C, Goldberg H, Kennedy DJ, Mandel S, Tyburski M, Sanders W, Sibell D, Smuck M, Wasan A, Won L, Jarvik JG. A randomized trial of epidural glucocorticoid injections for spinal stenosis. N Engl J Med 2014; 371 (1): 11-21. 7. Lakemeier S, Lind M, Schultz W, Fuchs-Winkelmann S, Timmesfeld N, Foelsch C, Peterlein CD. A comparison of intraarticular lumbar facet joint steroid injections and lumbar facet joint radiofrequency denervation in the treatment of low back pain: a randomized, controlled, double-blind trial. Anesth Analg 2013; 117 (1): 228-35. 8. Bogduk N. Degenerative joint disease of the spine. Radiol Clin North Am 2012; 50 (4): 613-28. 9. Bogduk N ed. Practice guidelines for spinal diagnostic and treatment procedures. 2nd edition. International Spine Intervention Society. San Francisco, USA 2013. 10. Park CH, Lee SH, Kim BI. Comparison of the effectiveness of lumbar transforaminal epidural injection with particulate and nonparticulate corticosteroids in lumbar radiating pain. Pain Med 2010; 11 (11): 1654-8. 11. Kennedy DJ, Plastaras C, Casey E, Visco CJ, Rittenberg JD, Conrad B, Sigler J, Dreyfuss P. 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; 15 (4): 548-55. 12. Dreyfuss P, Baker R, Bogduk N. Comparative effectiveness of cervical transforaminal injections with particulate and nonparticulate corticosteroid preparations for cervical radicular pain. Pain Med 2006 May-Jun; 7 (3): 237-42. 13. Lee JW, Park KW, Chung SK, Yeom JS, Kim KJ, Kim HJ, Kang HS. Cervical transforaminal epidural steroid injection for the management of cervical radiculopathy: a comparative study of particulate versus non-particulate steroids. Skeletal Radiol 2009; 38 (11): 1077-82. 14. El-Yahchouchi C, Geske JR, Carter RE, Diehn FE, Wald JT, Murthy NS, Kaufmann TJ, Thielen KR, Morris JM, Amrami KK, Maus TP. The noninferiority of the nonparticulate steroid dexamethasone vs the particulate steroids betamethasone and triamcinolone in lumbar transforaminal epidural steroid injections. Pain Med 2013; 14 (11): 1650-7.	Thank you for providing references. We reviewed them for inclusion in the report. All of the studies were either already included or did not meet inclusion criteria.
Reviewer 4	Discussion / Conclusion	I have outlined my disagreements with AHRQ methodology and the study conclusions in prior segments of this review. The authors compare their efforts to similarly constructed systematic reviews and meta-analyses that examine only data from randomized controlled trials, and unsurprisingly arrive at similar conclusions.	As the reviewer mentions, the points in this comment are described more specifically in other comments that we responded to in detail.

Commenter	Section	Comment	Response
Reviewer 4	Discussion / Conclusion	In the paragraph on applicability, the authors note the absence of qualifying controlled studies on epidural injections addressing sub-acute symptomatology, types of corticosteroids used, number and frequency of injections, utilization in the postoperative patient with radicular pain, and integration into comprehensive spine care. A failing of this assessment is that there is evidence available for examination from well-conducted non-controlled trials of transforaminal epidural steroid injections (TFESI) on all of these questions. They inform physicians and patients. They are not perfect evidence, but they provide information of greater clinical value than randomized controlled trials that fail to control for patient selection, standardized and optimized technical performance of procedures or measure categorical outcomes. To provide examples, the greater responsiveness of patients with sub-acute (versus chronic) radicular pain syndromes to TFESI was examined in a retrospective analysis of prospectively acquired data on 2024 consecutive lumbar TFESI injections. (1) The proportion of responders with sub-acute pain syndromes was 62% for pain reduction (50% improvement) and 59% for functional recovery (40% improvement on Roland-Morris) compared with 38% (pain) and 34% (function) in chronic pain patients (pain > 1 year). (1) The several studies addressing particulate versus non-particulate steroids, a critical topic ignored by this assessment, were detailed in the prior segment. The utility of repeat TFESI injections has been examined in several studies. A systematic review identified nine TFESI studies of disc herniation patients with categorical outcomes data; of patients achieving responder status (≥ 50% pain relief), 94% required only a single injection, 4% required two. Multiple injections are usually not necessary (2) A study of 3,645 consecutive lumbar TFESI demonstrated that the response in pain relief and functional recovery at two weeks post TFESI is strongly associated with longer term response, and is thus a rational time to consider repeat injection for incomplete responders, or surgical therapy for non-responders. (3) Another study of 6,582 consecutive lumbar TFESIs for disc herniations or fixed lesions demonstrated that within 1 year of an index injection, 22.4 % required an additional injection in hopes of cumulative benefit or recovery of benefit that had waned. 18% used a second injection, only 3.6% a third injection. (4) This study also demonstrated that early repeat TFESI (within 3 months of an index injection) provided statistically significant cumulative benefit to incomplete responders, and that patents	Thank you for your comment. Given the availability of over 50 trials of injections, we think trials to address these issues are feasible. We do not believe that observational data such as that taken from registries should trump evidence from well-conducted clinical trials. Well-conducted RCTs may be particularly important for evaluating effects on subjective outcomes such as pain, which is more susceptible to placebo effects.

Commenter	Section	Comment	Response
		with sub-acute pain syndromes undergoing repeat injections could expect complete restoration of relief achieved on an index injection which has since waned. (4) In a study of 156 patients with persistent radicular pain post surgical intervention, 31% (95% CI ± 7%) responded to a TFESI and none of these patients required revision surgery. (5) An another study, 69 patients who had failed conservative treatment and were awaiting surgery for chronic radicular pain were offered an integrated program of TFESI and physical therapy. (6) 78% avoided surgery in the subsequent year, with 62% having no pain or negligible pain (VAS < 10/100) and significant functional recovery (Roland–Morris scores < 3/24) at one year follow up. (6) Evidence exists. Although imperfect, it can assist in clinical decision-making.	
Reviewer 4	Discussion / Conclusion	Regarding limitations of the review process, I would prefer the authors at least acknowledge that the heterogeneity in diagnostic specificity and technical variation in procedural performance present in many of the studies were not considered in grading of the study quality. The inclusion of two to three decade old studies using techniques considered unacceptable in contemporary practice guidelines is a limitation of the process in this reviewer's judgment.	As described in previous responses, there was no evidence that effectiveness of injections varied according to the technique used. We also performed an additional analysis and found no effect on publication date and estimate of effectiveness. Specific technical factors were evaluated and none were found to impact conclusions.
Reviewer 4	Discussion / Conclusion	Regarding research gaps, the authors identify many of the important topics yet to be investigated in controlled trials. Evidence from non-controlled trials addresses several of these questions, as noted above, and can inform more rigorous controlled trials. Given the complexity of the issues, the cost involved in controlled trials, and the challenges in recruiting patients with debilitating pain into placebo controlled trials, it is likely that many of these gaps in evidence will never be examined as primary variables in controlled trials. Prioritization is key. In regard to radicular pain, trials of the efficacy, effectiveness and importantly efficiency (cost effectiveness) of TFESI when integrated into a comprehensive treatment approach would seem of the highest priority. There is already significant evidence in controlled and uncontrolled trials that TFESI have efficacy and clinical effectiveness in disc herniation patients- its cost effectiveness in the context of comprehensive spine care needs study. There must also be more rigorous comparison of such an integrated treatment against competing technologies to include cognitive behavioral therapy alone, pharmaceuticals, and surgery. Comparators must include clinical effectiveness, efficiency, and harms. Another priority would be assessing the effectiveness and efficiency of TFESI in the	Thank you for providing your thoughts on needed future research. Benefits of TFESI appear relatively modest and short-term. We revised the discussion to note that additional trials using patient selection and injection techniques considered optimal would be helpful for clarifying whether larger benefits are possible, and we believe this could be accomplished through a randomized trial. Trials could also be designed to assess subgroups noted. Cost-effectiveness is outside the scope of this review.

Commenter	Section	Comment	Response
		treatment of the elderly population with fixed lateral recess or foraminal stenosis causing radicular pain or radiculopathy. In this patient population, comparison with far-lateral, image guided interlaminar injections would be useful.	
Reviewer 4	Discussion / Conclusion	Any further study of epidural steroid injections in neurogenic claudication patients should focus on documentation of delivery of the pharmaceutical agent to the epidural space. It remains unclear from existing studies where the steroid was delivered.	The evidence indicates no clear differences in effectiveness based on the technique used and there was insufficient evidence to determine whether imaging guidance increases effectiveness. Therefore, we do not agree that this is necessarily a key research gap.
Reviewer 4	Discussion / Conclusion	The authors comment on the need to identify patients with facet joint pain to inform future studies. The mechanism exists: dual comparative medial branch blocks. A rigid diagnostic algorithm should be a predicate to any future study of facet interventions. The same applies for future studies of sacroiliac joint complex interventions. It must first be determined if the pain arises from within the joint (controlled intra-articular blocks) or the dorsal ligamentous complex (multi-site, multi-depth lateral sacral blocks, with negative intra-articular blocks) or both, before interventions are tested. Diagnosis must precede therapy.	As noted above, the accuracy of dual medial branch blocks for diagnosing facet joint pain is unknown because no reference standard exists. A randomized trial that compared effects of facet join radiofrequency denervation in patients selected on the basis of a dual block, single block, or no block found no differences in effectiveness. Therefore, we believe that there remains a need for studies to accurately identify patients with facet joint pain.
Reviewer 4	Discussion / Conclusion	Note: Page 47, lines 13-16. This sentence is incorrectly formulated. I assume it should read … epidural nonsteroid injections might be more effective than nonepidural injections…	We corrected the typo.
Reviewer 4	Discussion / Conclusion	References 1. Kaufmann TJ, Geske JR, Murthy NS, Thielen KR, Morris JM, Wald JT, Diehn FE, Amrami KK, Carter RE, Shelerud RA, Gay RE, Maus TP. Clinical effectiveness of single lumbar transforaminal epidural steroid injections. Pain Med 2013; 14 (8): 1126-33. 2. 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 (1): 14-28. 3. El-Yahchouchi C, Wald J, Brault J, Geske J, Hagen C, Murthy N, Kaufmann T, Thielen K, Morris J, Diehn F, Amrami K, Carter R, Shelerud R, Maus T. Lumbar transforaminal epidural steroid injections: does immediate post-procedure pain response predict longer term effectiveness? Pain Med 2014; 15 (6): 921-8. 4. Murthy NS, Geske JR, Shelerud RA, Wald JT, Diehn FE, Thielen KR, Kaufmann TJ, Morris JM, Lehman VT, Amrami KK, Carter RE, Maus TP. The effectiveness of repeat lumbar transforaminal epidural steroid injections. Pain Med 2014; 15 (10): 1686-94. 5. Klessinger S. Radicular pain in post lumbar surgery syndrome: the significance of transforaminal injection of steroids. Pain Med 2013; 14 (2): 243-6. 6. van Helvoirt H, Apeldoorn AT, Ostelo RW, Knol DL, Arts MP, Kamper SJ, van Tulder MW. Transforaminal epidural steroid injections followed by mechanical diagnosis and therapy to prevent surgery for lumbar disc herniation. Pain Med 2014; 15 (7): 1100-8.	Thank you for providing references. We reviewed them for inclusion in the report. None met inclusion criteria.

Commenter	Section	Comment	Response
Reviewer 4	Clarity / Usability	The most important judgment in this review of the AHRQ Technology Assessment on pain management injection therapies for low back pain is that of its utility in informing clinical practice decisions or public policy. I do not take this matter lightly. Regarding public policy, there can be no doubt that injection therapies for pain of spinal origin have been subject to overutilization, fraud and abuse. Although contemporary data suggest a recent damping of the rise in utilization of epidural steroid injections, the rapid increase in use in the late 1990s and in the decade of 2000-2010 merits concern and assessment. The raw utilization numbers fail to reveal an even more disturbing theme, the wide heterogeneity in practice patterns, suggesting that on a societal basis these procedures are often not being applied with appropriate care in patient selection, or performed with appropriate technical rigor. This is rooted in the lack of a clear and accountable educational and credentialing pathway for physicians who perform interventional procedures for pain of spinal origin. It is for this reason that I have spent countless hours over the past decade teaching and advocating for the use of only evidence based interventional pain procedures with initial rigorous diagnosis, followed by careful patient selection, meticulous technical performance, and with ongoing outcomes evaluation as an ethical imperative. I endeavor to conduct my clinical practice in this manner, teach my academic trainees in this manner, and teach and advocate for this within professional societies. It would appear then that there is an alignment between the concerns that motivated the undertaking of this technology assessment, and the evidence informed beliefs of this reviewer. This might be expected to produce a favorable response. This is sadly not the case. Unfortunately, lack of clarity in diagnosis, restrictive methodology, and lack of attention to patient selection, technical procedural performance, and valid outcomes measures results in several conclusions that I believe are unsupported and erroneous. I do not believe that this technology assessment should be the basis for clinical decision-making or public policy creation.	Thank you for your comment. The purpose of the review is to summarize the evidence, not to make clinical or policy recommendations. Regarding your assessment of the review, as described above, the characteristics that you describe are addressed in detail in the review. In addition, we do not believe that observational data such as that taken from registries should trump evidence from well-conducted clinical trials. Well-conducted RCTs may be particularly important for evaluating effects on subjective outcomes such as pain, which is more susceptible to placebo effects.

Commenter	Section	Comment	Response
Reviewer 4	Clarity / Usability	This is an assessment of therapeutic interventions. Well-founded therapeutic decisions are based on rigorous diagnosis. This assessment begins with the false premise that "low back pain" is overwhelmingly non-specific and not subject to specific diagnosis. This is untrue. Careful application of spinal diagnostic techniques can identify specific pain generators for both somatic axial pain and radicular pain. (1) Only with a specific diagnosis established should therapeutic interventions be applied. Unfortunately, many of the included studies fail to establish a diagnosis prior to intervention; this is not recognized as a study weakness in the assessment of study quality. The authors can, as do I, rightly critique the manner in which spinal injection techniques are applied in the US medical care system. This is, however, quite different from the conclusions reached that the techniques themselves provide no benefit.	Thank you for your comment. We examined effects of methods for selecting patients (e.g., use of imaging criteria, use of diagnostic injections) and there were no patterns suggesting that they affected the results.
Reviewer 4	Clarity / Usability	The restriction of included studies to randomized controlled trials excludes valuable observational studies that could enrich and expand the evidence base. As Dr. Sackett notes: "Evidence based medicine is not restricted to randomised trials and meta-analyses. It involves tracking down the best external evidence with which to answer our clinical questions. " (2) This is most evident in the failure to evaluate the several recent observational studies which buttress the controlled trial support for the use of transforaminal epidural steroid injections as a useful therapy for radicular pain due to disc herniations. The authors dismiss out of hand all but randomized controlled trials, despite evidence that "well-designed observational studies (with either a cohort or a case–control design) do not systematically overestimate the magnitude of the effects of treatment as compared with those in randomized, controlled trials on the same topic." (3) This is particularly problematic in that many of the included randomized controlled trials fail to establish a diagnosis prior to a therapeutic intervention, or do not rigorously control the technical performance of the procedures, or report only continuous outcomes. If the patient does not have the disease to be treated, or the technique utilized cannot document delivery an anti-inflammatory agent to the site of inflammation, what then is being studied? Continuous outcomes data will conceal segregation of the studied cohort into responders and non-responders. The selected literature is gilded by its randomized controlled methodology, even when it may be of no practical value. The need to maximize the pool of available controlled trials has resulted in the inclusion of irrelevant and archaic controlled studies that bear no relationship to current clinical	While observational studies can be useful for harms and in certain instances, as is discussed in the AHRQ Methods Guide, they are highly susceptible to confounding and bias have been shown to be misleading in the field of low back pain as well as in many other fields of medicine, particularly when evaluating the effectiveness of interventions based on subjective outcomes. Therefore, well-conducted randomized trials remain the standard for evaluating the effectiveness of interventions. We do not agree that observational studies should take precedence over higher-quality randomized trials. In addition, over 50 trials of injections exist; therefore, we do not agree that trials are lacking in this area. Please also note that a Topic Refinement Document with Key Questions and PICOTS (including restriction to RCTs) was posted for public comment.

Commenter	Section	Comment	Response
		practice. These factors went unrecognized, as the authorship did not include clinicians active in the field, who could have identified these deficiencies. When no randomized controlled trials were available for the key questions presented, as was the case for many of the questions addressed to epidural injections, and most of those for the facet and sacroiliac joint interventions, the authors simply noted "insufficient evidence." A better path was suggested by Dr. Sackett: "if no randomised trial has been carried out for our patient's predicament, we must follow the trail to the next best external evidence and work from there." (2) Our patients deserve this. Dr. Concato concurs: "The popular belief that only randomized, controlled trials produce trustworthy results and that all observational studies are misleading does a disservice to patient care, clinical investigation, and the education of healthcare professionals" concluding that "ignoring the evidence from observational studies is not a viable option". (3)	
Reviewer 4	Clarity / Usability	I wish to acknowledge the incredible effort required of the authors and their staffs to assemble, organize and evaluate the controlled studies presented in this technology assessment. I am in agreement with their stated motivation suggesting there is great need to assess, and constrain, the often excessive and improper utilization of interventions directed toward pain of spinal origin. I cannot agree with the methods utilized in this assessment, and hence its conclusions. Were this assessment used to define public policy, it could result in the inappropriate restriction of access to procedural techniques that are effective in relieving pain and effecting functional recovery in carefully selected patients. Without doubt, such restriction would reduce excessive and inappropriate utilization. Also without doubt, many patients would undeservedly suffer and see their lives diminished. It is unfortunate that the effort and expense involved in creation of this technology assessment could not have been utilized to fund well conceived studies, informed by both knowledgeable clinicians and stringent research expertise, that could have provided answers to the many key questions that remain largely unaddressed.	Thank you for your comment. The purpose of the review is to summarize the evidence, not to make clinical or policy recommendations. The reviewer is summarizing comments that have been presented earlier, that we responded to in detail.
Reviewer 4	Clarity / Usability	References 1. Bogduk N ed. Practice guidelines for spinal diagnostic and treatment procedures. 2nd edition. International Spine Intervention Society. San Francisco, USA 2013. 2. Sackett DL, et al. Evidence based medicine: what it is and what it isn't. BMJ 1996 Jan 13;312:71-72. 3. Concato J, Shah, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Engl J Med 2000;342:1887-9.	Thank you for providing references. We reviewed them for inclusion in the report. None met inclusion criteria.

Commenter	Section	Comment	Response
Reviewer 5	General Comments	I have reviewed the ex-summary on this topic. I found it comprehensive, informative, and helpful. It was extremely well done and complete. I think it confirms the current thought process on this topic. Rather than providing new information. The next step it seems to me is developing guidelines and payment criteria for the use of this procedure.	Thank you.
Reviewer 6	General Comments	This is one of the highest quality systematic reviews of interventions for musculoskeletal conditions I have reviewed. The questions are comprehensive, leading to a more complete review of the subject than has been previously published. Specific attention to the duration of effect is very useful. I feel that the report is balanced in its discussion of limitations.	Thank you.
Reviewer 6	Methods	I found the use of differential meta-analytic techniques, and the attention to outlier studies, very well done.	Thank you.
Reviewer 6	Methods	My only methodological issue relates to the exclusion of studies on harms that were observational and with smaller numbers. As the authors are fully aware, serious adverse events may be quite rare and not found in either RCTs or large observational studies. As it is, the review really points out no serious adverse events. A summary from one review: Multiple recent reports cite contaminated epidural steroid injections resulting in meningitis, stroke, paralysis, and death. The Center for Disease Control (CDC) specifically identified 25 deaths (many due to Aspergillosis), 337 patients sickened, and 14,000 exposed to contaminated steroids. Nevertheless, many other patients develop other complications that go unreported/underreported: Other life-threatening infections, spinal fluid leaks (0.4-6%), positional headaches (28%), adhesive arachnoiditis (6-16%), hydrocephalus, air embolism, urinary retention, allergic reactions, intravascular injections (7.9-11.6%), stroke, blindness, neurological deficits/paralysis, hematomas, seizures, and death. None of these serious adverse events is addressed in this report.	Thank you for your comment. Large controlled observational studies of harms were included. Case series and reports were not included because it is not possible to determine comparative risks from them. However, case reports of serious complications from spinal injections are noted in the Discussion.
Reviewer 6	Results	See above comments Re harms	Noted.
Reviewer 6	Discussion / Conclusion	Balanced, solid discussion and conclusion	Thank you.
Reviewer 6	Clarity / Usability	Very clear and usable	Thank you.
Reviewer 7	General Comments	This is a rigorously conducted and clearly reported systematic review. The topic and findings are clinically meaningful and should be useful to clinicians making decisions about therapeutic options. The target population and interventions are clearly	Thank you.

Commenter	Section	Comment	Response
		defined. The key questions are appropriate and clearly stated.	
Reviewer 7	Introduction	The introduction concisely summarizes the problem of low back pain and trends in utilization of injection therapies. It also provides a helpful summary of relevant prior reviews and guidelines.	Thank you.
Reviewer 7	Methods	Overall, the eligibility criteria, search strategies, and analysis methods are appropriate and well described.	Thank you.
Reviewer 7	Methods	It would be helpful if the definition of the “success” outcome was more explicitly described (page 8, line 37). The authors imply, but do not explicitly state, that “success” was as defined by each trial.	Thank you for your comment. We revised the Methods to clarify that "success" outcomes were as defined in the individual trials. The Results section describes the specific definitions used in the trials.
Reviewer 7	Results	Overall, the results are clearly described and summarized. The key messages are clear and clinically relevant. I am not aware of any studies that were overlooked or incorrectly included/excluded.	Thank you.
Reviewer 7	Results	Pages 15 (last paragraph), 131 (Table 12), and G-6 (Appendix G): For immediate improvement in pain with epidural injection vs. placebo in spinal stenosis, the conclusion (no difference) does not seem to match the provided results (mean difference –22.0, 95% CI –36.0 to –8.0). Should the 95% CI be “-36.0 to 8.0”?	The results are reported correctly; we revised so that it is clearer that injection was superior at pain at immediate-term, but results were based on a single trial.
Reviewer 7	Discussion / Conclusion	The findings are clearly summarized and their implications are appropriately stated. Comparisons with prior reviews are concisely and clearly discussed. Limitations are adequately described. I am not aware of any important literature that was omitted. The future research section is clear and suggests feasible research directions.	Thank you.
Reviewer 7	Clarity / Usability	Overall, the report is clear and well organized. Prespecification of clinically relevant differences for commonly reported outcome measures is particularly helpful for interpretation of findings. Conclusions should be useful for informing policy and practice decisions.	Thank you for your comment.
Reviewer 7	Clarity / Usability	Minor comment: Describing findings in terms of immediate, short, intermediate, and long-term outcomes is clinically useful. Clarity of this terminology could potentially be improved if “intermediate term” to was changed to “medium term.” As a sometimes hasty reader, I found myself tripping over the similarity of the words “immediate” and “intermediate.”	Thank you for your comment. We left the terminology as "intermediate-term," as only one reviewer mentioned this point, and a recent review published in Annals of Internal Medicine (by Pinto et al.) used similar terminology.

Commenter	Section	Comment	Response
Reviewer 8	General Comments	This is not as clinically meaningful as it should be given the importance of this subject- the weaknesses of applying the methodology used to generate this report in applying findings to individual patients should have been disclosed	Thank you for your comment. The purpose of the review is to summarize the evidence, not to make clinical or policy recommendations.
Reviewer 8	Introduction	Fine	Thank you.
Reviewer 8	Methods	You are summarizing studies NOT individual patient care- it is what it is- the mistake is in thinking you can apply this methodology to the patient in front of you	Thank you for your comment. The purpose of the review is to summarize the evidence, not to make clinical or policy recommendations.
Reviewer 8	Results	Sure	Thank you.
Reviewer 8	Discussion / Conclusion	Limitations from a research viewpoint are well described BUT those do not translate into patient care	Thank you for your comment. The purpose of the review is to summarize the evidence, not to make clinical or policy recommendations.
Reviewer 8	Clarity / Usability	The report is structured to be biased against the tenets of clinical practice- therefore although well written, its conclusions should not on their own be used to inform policy and/or practice decisions	Thank you for your comment. The purpose of the review is to summarize the evidence, not to make clinical or policy recommendations.
Public Reviewers			
Theresa Dews, MD Cleveland Clinic	General Comments	Excellent review however the limitations were well outlined by the authors. As a clinician who performs these procedures in well selected patients as part of a comprehensive pain management treatment program, I'm concerned that the limited evidence outlined will negatively impact patients who do improve with appropriate treatment.	Thank you for your comment. The purpose of the review is to summarize the evidence, not to make clinical or policy recommendations.
Theresa Dews, MD Cleveland Clinic	General Comments	Insurance companies will use this to restrict availability of treatment for appropriate patients.	Thank you for your comment. The purpose of the review is to summarize the evidence, not to make policy recommendations.
Daniel Cher, MD SI-BONE, Inc.	General Comments	The objective of the document is to summarize the safety and effectiveness of steroid injections in the spine for chronic pain. Outside of the scope of review is the use of local anesthetic blocks used to confirm the blocked body location as a pain generator. In many of the studies cited in the current review, diagnostic blocks were used to select study subjects.	Thank you for the comment. We evaluated how use of diagnostic injections to select patients for facet joint injections impacted findings, but the accuracy of diagnostic blocks was beyond the scope of the review.
Daniel Cher, MD SI-BONE, Inc.	General Comments	Executive Summary: An additional section could be added at the end of this section on the use of diagnostic blocks.	The accuracy of diagnostic blocks was outside the scope of this review.
Daniel Cher, MD SI-BONE, Inc.	General Comments	**Outside of Scope** Outside of the scope of this document is the use of local anesthetic blocks to confirm the blocked body location as a pain generator. In many of the studies cited in the current review, diagnostic blocks were used to select study subjects.	The accuracy of diagnostic blocks was outside the scope of this review.

Commenter	Section	Comment	Response
Daniel Cher, MD SI-BONE, Inc.	Introduction Background	A sentence could be added: The use of local anesthetic blocks to diagnose a body location as a pain generator is outside of the scope of this review.	We added a sentence to the methods that studies on the diagnostic accuracy of diagnostic blocks was outside the scope of the review, though the review evaluated how use of diagnostic blocks to select patients impacted effectiveness.
Daniel Cher, MD SI-BONE, Inc.	Results	Two additional studies on SI joint steroid injection could be cited: Luukkainen randomized 20 patients with SI joint dysfunction to periarticular injection of methylprednisolone (1.5 cc of 40 mg/ml) and lidocaine (1.5 cc) vs. isotonic saline (1.5 cc) and lidocaine (1.5 cc). Patients in the steroid group had a larger change in VAS pain ratings and pain index scores at two months (both p<.05). Patients were blinded to treatment assignment. Maugars randomized 10 patients with 13 painful SI joints due to ankylosing spondylitis to cortivazol (1.5 cc) or isotonic saline. Both the injecting physician and subject were blinded to treatment. At one month after injection, pain was reduced 82 points in the steroid group and 18 points in the control group (p=0.003). Combined with the cited study on SI joint steroid injection, the evidence supporting short term pain relief upon steroid injection of the SI joint pain is moderate. Citations: Luukkainen: Clinical and Experimental Rheumatology 1999; 17: 88-90 Maugars: British Journal of Rheumatology 1996;35:767-770 These studies may meet the document's criteria for study selection. The review cited only one trial of steroids for SI joint pain treatment. However, 3 well-done randomized trials have been published. Three trials of SI joint steroid injection provide more evidence of effectiveness than cited in the current document. The summary table could be changed to include a meta-analytic summary of the 3 cited studies. The amount of evidence could be changed from "insufficient" to "low."	These trials were excluded because they evaluated sacroiliac joint injections for spondylarhtropathy (an excluded condition).

Commenter	Section	Comment	Response
David Vaughn Anesthesia Services of Lynchburg	General Comments	Comment Regarding the History AHRQ's Analyses in Another Area of Medicine: Thank you for the opportunity to comment on this review. Thank you also to the committee for their hard work in trying to determine efficacy of these interventions. My comments in this first area, I suspect, will stand alone among those offered. I wish to make it clear that the conclusions of the committee may be wrong. The data may simply be insufficient to yield a valid conclusion. Important errors have been made by AHRQ previously. I care for patients with neck and back pain, providing injections in the epidural space. I trained in anesthesiology, and continue to provide anesthesia care. Within the area of perioperative medicine, I developed an interest many years ago in a clinical question - perioperative beta blockade. This question involved the administration of beta-blockers to patients at risk for cardiac events during the perioperative period. Several small studies conducted in the mid-nineties suggested enormous benefit. Other small studies followed. Meta-analyses followed. Clinicians were analyzing, debating, and editorializing. Expert consensus on the available data favored the strong benefit of beta blockade. Papers followed that detailed the lack of widespread compliance to this practice, the implication being that clinicians needed to "get with the guidelines." Regarding action at the national level, I was told that the administration of beta-blockers was nearly included in the SCIP mandates for evidence-based perioperative care. Beta-blocker administration fortunately was excluded from those mandates, except for the continuation of beta-blockers for patients who had been taking beta-blockers previously. AHRQ also weighed in. In 2003, this statement appeared on the AHRQ website (the link is: http://archive.ahrq.gov/research/findings/evidence-based-reports/services/quality/er43/ptsafety/epcsummary.html)	Thank you for your comment; however, the report mentioned is not relevant to this topic.

Commenter	Section	Comment	Response
David Vaughn Anesthesia Services of Lynchburg	General Comments	Continued- Clear Opportunities for Safety Improvement The following 11 patient safety practices were the most highly rated (of the 79 practices reviewed in detail) in terms of strength of the evidence supporting more widespread implementation. Practices appear in descending order, with the most highly rated practices listed first. Because of the imprecision of the ratings, the editors did not further divide the practices, nor indicate where there were ties. Appropriate use of prophylaxis to prevent venous thromboembolism in patients at risk. Use of perioperative beta-blockers in appropriate patients to prevent perioperative morbidity and mortality." (followed by 9 more practices. - RV) This was quite an endorsement. AHRQ concluded that perioperative beta blockade was more important than other medical interventions like administration of certain vaccines, or protocols for avoiding retained foreign bodies or preventing wrong-site surgery. Unfortunately, the endorsement was dangerously incorrect. In 2008, the largest RCT studying perioperative beta blockade was published: the POISE paper (n=8351) appeared in the 5/12/08 issue of Lancet. Overall, POISE did not show benefit for patients at reasonably high risk who got an aggressive protocol of perioperative metoprolol. POISE showed harm. Some measures (stroke) were higher in the treatment group than placebo, although fewer patients in the metoprolol group had a myocardial infarction (4.2% vs. 5.7% p=.0017.) Overall mortality was significantly higher in the beta-blocked group (3.1% vs. 2.3%; p=.03.) The POISE trial has been criticized for a high dose of metoprolol. Interestingly, other trials of betablockers that didn't yield benefit were criticized for an insufficiently low dose of metoprolol. Nevertheless, a definitive trial had concluded that aggressive beta blockade resulted in increased mortality.	Thank you for your comment; however, the report mentioned is not relevant to this topic.

Commenter	Section	Comment	Response
David Vaughn Anesthesia Services of Lynchburg	General Comments	Continued- If AHRQ had been successful in "supporting more widespread implementation," best evidence suggests that lives would have been lost. AHRQ's absolute certainty that beta -blockade saved lives was absolutely wrong. The number needed to harm - the harm being mortality - was about 100. With millions (twenty?) of surgeries performed each year in the US, the harm might have amounted to thousands, or tens of thousands of patients. In response to the POISE trial, the American College of Cardiology, with it's own analysis of data, stated: "In light of the POISE results, routine administration of perioperative beta blockers, particularly in higher fixed-dose regimens begun on the day of surgery, cannot be advocated. " This history of inaccurate AHRQ analysis and conclusions, potentially leading to harm instead of benefit, should serve as a cautionary tale to those evaluating the current topic. It is reasonable, in fact- critical, for careful analysis of available data to be undertaken. As well, the validity of the conclusions perhaps may be best defined in detailing levels of confidence in the conclusions (in this area, I would submit - low -virtually across the board), rather than in the conclusions themselves. I strongly encourage caution in presenting conclusions based on the available data regarding interventional spinal injections.	Thank you for your comment; however, the report mentioned is not relevant to this topic.
David Vaughn Anesthesia Services of Lynchburg	General Comments	Comments Regarding this AHRQ Analysis: -Most importantly, the AHRQ needs to call for more large trials that would help direct this area of medicine. -This analysis does not stand alone. In particular, the consensus of fourteen medical societies whose members provide spinal injections favors the benefit of injections. The societies' letter (November 2014) to the FDA regarding efficacy can be found here: http://1515docs.org/pdfs/Multisociety_ESI_Letter_to_FDA_11-7-2014.pdf -Virtually all clinicians I know agree that ESI and medial branch blocks/RF are over-utilized. Virtually all clinicians I know agree that ESI and medial branch blocks/RF do help select patients. The analysis should accept these observations as valid, and use them to inform their appraisal of the relatively scant data from clinical trials.	Thank you for your comment. The report here is based on a synthesis of the best available evidence; opinions from professional organizations are not considered evidence. In addition, some organizations (e.g., American Academy of Neurology) do not recommend routine use of epidural steroid injections.

Commenter	Section	Comment	Response
David Vaughn Anesthesia Services of Lynchburg	General Comments	In Summary I am grateful for the opportunity to provide feedback. AHRQ is on record with at least one analysis that turned out to be critically incorrect, as more definitive data became available. A consensus of fourteen medical societies whose members employ spinal injections to help patients have conducted their own analysis, and find that in carefully selected patients these injections have benefit. Thank you again to the committee for their efforts on behalf of our patients.	Thank you for your comment; however, the first report mentioned is not relevant to this topic. The second report mentioned is based on a synthesis of the best available evidence; opinions from professional organizations are not considered evidence. In addition, some organizations (e.g., American Academy of Neurology) do not recommend routine use of epidural steroid injections.
Andrew J. Engel, MD	Methods	The recent report from the Agency for Healthcare Research and Quality (AHRQ), on Pain Management Injection Therapies for Low Back Pain (1), has significant methodological flaws that make validation of its conclusions impossible. By failing to include all studies, mixing study types, and including injections that are not target-specific, this putative analysis of the literature would not pass peer-review in an evidence based pain journal such as Pain Medicine. The minimum standards for a review paper have already been published. (2)	Thank you for your comment. This reviewer is summarizing comments that are presented in more detail below, where we respond to each comment.
Andrew J. Engel, MD	Methods	Failure to Include All Relevant Studies Failing to include all studies introduces the risk of bias. That bias comes from both ignoring high quality observational studies and not including all of the published randomized controlled trials (RCT). Many accepted treatments in medicine have not been validated by randomized placebo controlled trials (e.g. insulin, joint replacement). It could be unethical to subject patients to RCTs when the magnitude of effect of the treatment is so large. Therefore, some of the best available evidence consists of high quality observational studies. Looking at all the high quality published data therefore is the standard. The Centers for Disease Control and Prevention uses Grading the Recommendations of Assessment, Development, and Evaluation (GRADE) since it is a peer-reviewed, transparent, and comprehensive tool for assessing the quality of a body of evidence. (3) When using GRADE, if specific criteria are met (e.g., high magnitude of health effect, dose-response gradient), the data from methodologically-sound, observational studies can be upgraded to high quality evidence, the same level of evidence provided by RCTs. (4) When one well-respected government agency uses a tool to assess literature, that instrument should at least be considered by other government agencies. If there were disagreement about the current standard in determining the quality of literature, surely the tool that has	Thank you for your comment. While observational studies can be useful for harms and in certain instances, as is discussed in the AHRQ Methods Guide, they are highly susceptible to confounding and bias have been shown to be misleading in the field of low back pain as well as in many other fields of medicine, particularly when evaluating the effectiveness of interventions using subjective outcomes. Therefore, well-conducted randomized trials remain the standard for evaluating the effectiveness of interventions. We do not agree that observational studies should take precedence over higher-quality randomized trials. In addition, over 50 trials of injections exist; therefore, we do not agree that trials are lacking in this area. Please also note that a Topic Refinement Document with Key Questions and PICOTS (including restriction to RCTs) was posted for public comment. We assessed the strength of evidence for each Key Question and outcome using the approach described in the AHRQ Methods Guide, which includes consideration of the precision of estimates (which is affected by the sample size). The details of the process are described in the Methods and presented in Table A, Table 12, and Appendix G (Strength of Evidence). The Maugars study did not meet inclusion criteria because it evaluated patients with spondylarthropathy, an excluded condition.

Commenter	Section	Comment	Response
		been subjected to peer-review would be the criterion standard until a superior instrument surpasses it. Some might argue that omitting data from observational studies is appropriate because of the artificially high success rate of treatments that have not been subjected to RCTs. If the logic behind the search strategy is clearly explained, it?s not unreasonable to restrict the search to RCTs, however, the review is no longer comprehensive. What is not acceptable is to ignore data. A cursory review of the AHRQ report demonstrates at least one missing paper since the cause of low back pain was outside of the search criteria. (5) Failing to write a comprehensive review introduces a bias that cannot be overcome. The authors of the AHRQ report could argue that the data from the missing paper is not important because there were very few subjects. The subject number is not a relevant argument. In Maugers et al. there are only 10 subjects: 5 in the treatment group and 5 in the placebo group. The confidence intervals of the success rate do not overlap. (5) If there were 50, 500, or even 5000 patients in each group, we can surmise with 95% confidence that intra-articular steroid sacroiliac joint injections would still help patients. The treatment is so efficacious that it only took 5 patients in each group to find the effect.	
Andrew J. Engel, MD	Methods	Study Designs and Limitations While the AHRQ report only reviews a select group of RCTs, they consider all included RCTs as homogeneous. The data provided by this heterogeneous group of RCTs should be separated into two distinct categories of RCTs: pragmatic and explanatory studies. Pragmatic studies are designed to address questions about comparison of two or more treatments, while explanatory studies provide evidence about whether an active treatment is better than non-specific (placebo) effects. A review of high quality observational studies answers whether the treatment under study works in the real world. The explanatory studies only add information: whether the treatment itself works or whether the positive outcome occurred because of non-specific effects. It's tempting to review only RCTs because traditionally they are of higher quality than observational studies, but that statement is not universally true.	Thank you for your comment. We analyzed RCTs that evaluated injections versus a placebo intervention (epidural or nonepidural saline or local anesthetic) separately from trials that compared different active injections. RCTs are well-suited for evaluating comparative effectiveness. We do not believe that observational data such as that taken from registries should trump evidence from well-conducted clinical trials. Well-conducted RCTs may be particularly important for evaluating effects on subjective outcomes such as pain, which is more susceptible to placebo effects.

Commenter	Section	Comment	Response
Andrew J. Engel, MD	Methods	Data Analysis Limitations Finally a review of the data must review the data. Though this declaration seems intuitively obvious, clearly it?s not. Without society support or a previously scheduled sabbatical, it would be nearly impossible for a physician to practice evidence-based medicine (the quality of care the AHRQ manuscript purports to support) and review a 539-page document in 2 weeks. Therefore these comments will again focus on sacroiliac joint injections. The sole RCT cited is in fact not an RCT of intraarticular sacroiliac steroid injections - the accepted standard. The authors performed peri-articular steroid injections. (6) Peri-articular steroid injections have not been validated and are not part of common practice. An interventional pain management physician would not purposely place steroid next to the sacroiliac joint, just as an interventional cardiologist would not place a stent next to the atherosclerotic plaque. Target specificity is paramount. (7) The available data cited in the review are not insufficient; the review is insufficient. Combining evidence on heterogeneous injections (e.g. blind and image-guided, interlaminar and transforaminal) is a very common mistake made in systematic reviews and technology assessments, which results in decreasing the perceived effectiveness of a treatment. Pinto et al. (9) made this exact error when arriving at the same conclusion that epidural steroid injections give clinically insignificant short-term benefit. This mistake has already been called out. (10) In fact, Figure 3 of the AHRQ report unequivocally demonstrates a difference between transforaminal steroid injections and all other approaches to the lumbar epidural space for radiculopathy!	We included the only trial of sacroiliac injections for nonspondylarthopathic pain, and described the technique used. There is no evidence on other "ideal" sacroiliac joint injection techniques for nonspondylarthopathic pain.
Andrew J. Engel, MD	Methods	Expert Input and Peer Review Process Though the AHRQ report begins an important discussion about the current state of the evidence regarding interventional pain management in the United States, the methodological flaws make any conclusions or recommendations based on this report irrelevant to clinical practice. Yet, simply criticizing a review doesn't bring us closer to an answer. There must be a reason why this report fails. It could be that the authors are not experts. (8) The list of peer reviewers was redacted; therefore it is unclear whether appropriate expertise was sought or considered prior to publishing the draft report. An appropriate expert panel should include some interventional pain management experts to ensure the report is comprehensive and actually reviews the relevant literature. This peer review process and consideration of feedback should occur before the draft is	Thank you for your comment. It is standard AHRQ procedure to redact the list of peer reviewers of the draft report until the report is final. As part of AHRQ's topic refinement procedure, the protocol (scope of the report) was created with the input of CMS, Key Informants (including experts in the field), and the public.

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		prepared for public comment. An inordinate effort was wasted by the authors on assessing effectiveness of steroids for facet pain. It would seem impossible that a board certified interventional pain management physician would consider steroid for facet disease. For nearly a decade the data on intra-articular steroid facet injections has been clear ? placebo injections work better (11). For nearly half a decade the data that medial branch nerves do not respond to steroid has been known. (12) Just as neurosurgeons do not review the data on lobotomies, interventional pain management physicians do not review the data on steroids for facet disease. Until an accurate and comprehensive report written with expert involvement using an accepted instrument to determine the quality of literature has been subjected to peer-review, all you have is an opinion piece similar to these remarks.	
Andrew J. Engel, MD	Methods	References: 1. AHRQ report. http://www.ahrq.gov/research/findings/ta/call-for-public-review.html 2. Engel A, King W, MacVicar J, and on behalf of the Standards Division of the International Spine Intervention Society. 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. 3. Umscheid C, Agarwal R, P Brennan, for the Healthcare Infection Control Practices Advisory Committee (HICPAC). Updating the Guideline Methodology of the Healthcare Infection Control Practices Advisory Committee (HICPAC). The Department of Health & Human Services and The Centers for Disease Control. 4. Guyatt G, Oxman A, Kunz R, Vist G, Falck-Ytter Y, Sch?nemann H, and for the GRADE Working Group. What is "quality of evidence" and why is it important to clinicians? BMJ 2008;336;995-998. 5. Maugars, Y., Mathis, C., Berthelot, J. M., Charlier, C. & Prost, A. Assessment of the efficacy of sacroiliac corticosteroid injections in spondylarthropathies: a double-blind study. Br. J. Rheumatol. 1996;35:767?770. 6. Luukkainen RK, Wennerstrand PV, Kautiainen HH, et al. Efficacy of periarticular corticosteroid treatment of the sacroiliac joint in non-spondylarthropathic patients with chronic low back pain in the region of the sacroiliac joint. Clin Exp Rheumatol. 2002;20:52-54. 7. Engel A, MacVicar J, Bogduk N. Philosophical Foundation for Diagnostic Blocks, with Criteria for Their Validation. Pain Med. 2014;15:998-1006. 8. Bogduk N. Editor's Response: Group vs Categorical Data in Epidural Studies. Pain Med. 2014;15:1812-1813. 9. Pinto RZ, Maher CG, Ferreira ML, et?al. Epidural corticosteroid injections in the management of sciatica: A systematic review and meta-analysis. Ann Intern Med 2012;157(12):865?877. 10. Nampiaparampil D, Engel A. A Response to Two Recent Reviews of Epidural Steroid Injections. Pain Med. 2013;14:954-955. 11. Bogduk N. A Narrative Review of Intra-Articular Corticosteroid Injections for Low Back Pain. Pain Med 2005;6:287-296. 12. Manchikanti L, Singh V, Falco FJ, Cash KA, Pampati V. Evaluation of lumbar facet joint nerve blocks in managing chronic low back pain: a randomized, double-blind, controlled trial with a 2-year follow-up. Int J Med Sci. 2010;7:124-135.	Thank you for providing references We reviewed them for inclusion in the report. All were either already included or did not meet inclusion criteria.
Jeffrey Summers, MD International Spine Intervention	Methods	We commend the authors for reviewing and synthesizing a large volume of literature. There are however major flaws in the methodology of this report that significantly limit its usefulness.	Thank you for your comment. We reply to your more specific comments as they are outlined below.

Commenter	Section	Comment	Response
Society			
Jeffrey Summers, MD International Spine Intervention Society	Methods	Corruption of Evidence Based Medicine (EBM) Principles The work group appeared to take the proverbial high ground by their sole utilization of randomized controlled trials (RCTs) for determination of clinical effectiveness of injectable corticosteroids. This is unfortunately a corruption of evidence based medicine, which demands the utilization of the best available evidence, not only RCTs. This is exemplified by Sackett, who stated: "Evidence based medicine is not restricted to randomized trials and meta-analyses. It involves tracking down the best external evidence with which to answer our clinical questions."1 Therefore it is imperative that all well-designed and implemented studies that provide categorical data, as opposed to means of continuous data, on outcome measures including pain relief, functional outcomes, decreased use of other health care, surgery-sparing effects, and decreased use of opioids are required to inform for which patient subgroups a given intervention may be effective. Concato found that "well-designed observational studies (with either a cohort or a case control design) do not systematically overestimate the magnitude of the effects of treatment as compared with those in randomized, controlled trials on the same topic."2 Concato stated, "The popular belief that only randomized, controlled trials produce trustworthy results and that all observational studies are misleading does a disservice to patient care, clinical investigation, and the education of healthcare professionals? and that "ignoring the evidence from observational studies is not a viable option".2 An evidence base comprised of well-designed and implemented observational studies on consecutive patients can yield moderate to high quality evidence in accordance with GRADE. Unless multiple high quality RCTs with appropriately selected patients and technically accurate injections are available, observational studies should not be excluded from a comprehensive systematic review. This work group's decision to utilize only RCTs is unfortunate, as there are multiple, methodologically rigorous studies which included large cohorts of consecutive subjects that offer additional insights into the clinical effectiveness of these procedures.	Thank you for your comment. While observational studies can be useful for harms and in certain instances, as is discussed in the AHRQ Methods Guide, they are highly susceptible to confounding and bias have been shown to be misleading in the field of low back pain as well as in many other fields of medicine, particularly when evaluating the effectiveness of interventions based on subjective outcomes. Therefore, well-conducted randomized trials remain the standard for evaluating the effectiveness of interventions. We do not agree that observational studies should take precedence over higher-quality randomized trials. In addition, over 50 trials of injections exist; therefore, we do not agree that trials are lacking in this area. Please also note that a Topic Refinement Document with Key Questions and PICOTS (including restriction to RCTs) was posted for public comment.

Commenter	Section	Comment	Response
Jeffrey Summers, MD International Spine Intervention Society	Methods	Any literature review that is restricted to RCTs must come with an appropriate warning. The warning should include that limiting the review to RCTs skews the results to only those findings from RCTs and does not provide a balanced view of the published literature. As a result, it should also specify that the results of the review are not sufficient to inform treatment guidelines or policy. For this reason, multispecialty societies such as the North American Spine Society and the International Spinal Intervention Society have developed treatment guidelines stemming from a full assessment of the published literature. Such guidelines are appropriately constructed to inform medical treatment decisions and health policy. Restricting a technology assessment to only RCTs ignores many high-quality observational studies. Specific to an assessment of spinal injection therapies, many high-quality studies are excluded from this review. These studies provide important evidence regarding the use of spinal interventions; for example, prospective observational studies show good short-term and long-term (one year) outcomes for lumbar transforaminal epidural injections3 and lumbar facet joint injections4. These findings are supported by very large retrospective studies with high quality data, such as a Mayo Clinic study involving >2,000 subjects.5 These are just a few examples, and many other examples exist. All are ignored in the AHRQ technology assessment. While the studies just cited involve patients with different low back symptoms, they all share one important feature. The study populations are well-defined. The populations are not simply characterized by a symptom, such as back pain or sciatica. They have a radiographically confirmed pathoanatomic diagnosis that is responsible for their symptoms. This is a critical issue in the assessment of any study involving a targeted intervention.	Thank you for your comment. As already mentioned, while observational studies can be useful for harms and in certain instances, as is discussed in the AHRQ Methods Guide, they are highly susceptible to confounding and bias have been shown to be misleading in the field of low back pain as well as in many other fields of medicine, particularly when evaluating the effectiveness of interventions based on subjective outcomes. Therefore, well-conducted randomized trials remain the standard for evaluating the effectiveness of interventions. We do not agree that observational studies should take precedence over higher-quality randomized trials. In addition, over 50 trials of injections exist; therefore, we do not agree that trials are lacking in this area. The purpose of this report is to summarize the best available evidence, not provide policy or clinical recommendations.
Jeffrey Summers, MD International Spine Intervention Society	Methods	In addition to the work group's mistake in limiting this review to RCTs, it is imperative to recognize that study methodology is meaningless unless the procedures being assessed are performed on appropriately selected patients using accurate 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 and the procedure was not conducted accurately. Stratification of studies by 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. There are also other significant concerns regarding methodology	Thank you for your comment. We examined the factors mentioned; there were no findings to suggest that the patient or technical factors mentioned impacted results or conclusions.

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		that must be taken into consideration including: underlying diagnosis and its natural history, heterogeneity of procedural techniques along with the use of imaging, and even statistical analysis.	
Jeffrey Summers, MD International Spine Intervention Society	Methods	Inadequate Assessment by Diagnosis It is imperative to recognize that low back and radicular pain are merely symptoms, not diagnoses. Investigations of targeted injection therapies based on patients with a specific anatomic diagnosis repeatedly demonstrate high success rates for clinically meaningful changes in back pain and disability.6,7 Alternatively, spinal injections that treat back pain without a confirmed anatomic diagnosis yield poor results.8 The distinction here is of great importance to patients with back pain, but was not adequately accounted for by the authors of the AHRQ report who repeatedly inappropriately combined diagnostic etiologies. Of the 29 studies comparing epidural steroid injections to placebo, 22 specified radicular pain alone, six included a mixture of radicular and back pain, and one study included patients with back pain alone. For perspective, imagine a hypothetical systematic review of prescription medication for the treatment of cough, a symptom. A few studies may show beneficial effects from antibiotics in a group of patients with bacterial pneumonia, a specific diagnosis, whereas pooled data from heterogeneous groups ? 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?	We describe the patient populations and their diagnoses as it is reported in the studies. Key question 2 addresses how patient and other characteristics impact responsiveness to injections; as described, there was insufficient evidence to determine whether the cause of radicular symptoms, duration of symptoms, imaging findings, or other patient factors, or no clear association. In addition, to clarify, we stratified results for patients with radicular pain, non-radicular pain, and spinal stenosis separately.
Jeffrey Summers, MD International Spine Intervention Society	Methods	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. 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 spinal stenosis, which is less likely to resolve spontaneously with time. Thus short-term relief, as noted by the authors of the AHRQ report, would be very appropriate and expected for 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, as it is likely that 6-12 months following an infection all patients are better regardless of the treatment regimen. Again, should we withhold all antibiotics for	Thank you for your comment. We specifically analyzed outcomes at prespecified time points (immediate, short-term, intermediate, and long-term).

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		pneumonia given the favorable natural history, or should we state antibiotics are ineffective because all subjects were better at one 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?	
Jeffrey Summers, MD International Spine Intervention Society	Methods	The work group?s Key Question #1 epitomizes the fallacy of the lack of stratification by diagnosis. This question asks ? In patients with low back pain, what is the effectiveness of ?? Based on the logic presented, it is unclear why in 2014 this group chose to evaluate a symptom that is representative of a variety of diagnostic etiologies. While the authors did state that they considered factors that may present a favorable outcome, they clearly included studies in their analysis that evaluated symptoms rather than diagnoses. In order to justify this approach the authors note that: ?In the majority (>85%) of patients with low back pain, symptoms cannot be attributed to a specific disease or spinal pathology.? Their reference for this statement was an article from 20029, however this article is not the original source of data for this statement. The original source of this statement was actually a synopsis of a workshop on idiopathic low back pain from 1982.10 That article was not an original research study, and contained no original data or further references, and appears to have been an expert opinion. In that original article from 1982, the authors did note that ?estimates of the proportion of all low-back pain that has no definite etiology range widely from about 20% to 85%?. Thus in an effort to justify their approach by symptoms rather than specific diagnoses, the authors of the AHRQ report misquoted a 30 year-old opinion piece. They also relied on a manuscript that predates both modern MRI scanning and the current use of image-guided diagnostic injections, both of which have been repeatedly shown to assist in the diagnosis of spine pathology. Similarly the authors utilize literature from 20-30 years ago that merely evaluated a symptom-based population with non-specific techniques including blind injections. While this literature was appropriate and cutting edge at the time of publication, it is not reflective of modern medicine. To the contrary, current literature contains studies that have replicated prevalence estimates for sources of low back pain.11-17	As noted in the Introduction, the presence of imaging abnormalities is a poor predictor of the presence or severity of low back pain, and there is no reliable reference standard with which to determine the accuracy of "specific" diagnoses for most non-radicular low back pain. In addition, the statement does not apply to radicular back pain, the subject of the majority of trials in this report, which does have specific imaging and clinical findings. We assessed how use of imaging to identify patients with radiculopathy for inclusion impacted results (there were no clear effects).

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Jeffrey Summers, MD International Spine Intervention Society	Methods	Inadequate Accounting for Advances in Procedural Technology Similar to the inappropriate lumping of underlying diagnostic etiologies is the inappropriate lumping of procedural techniques -- specifically the use of image guidance. The reliable placement of steroids into the epidural space requires image guidance. The failure rate of ?blind? (non-image-guided) needle placement has been studied by several authors. Even in experienced hands, injection of contrast after blind needle placement, demonstrated needle placement during epidural injections was incorrect 25% of the time.18	Thank you for your comment. 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 or in head-to-head trials of transforaminal versus other approaches.
Jeffrey Summers, MD International Spine Intervention Society	Methods	Continued - Stitz determined in a study of 54 consecutive caudal injections without fluoroscopic guidance, successful injection placement on the first attempt occurred in 74.1% of the patients.19 Renfrew also prospectively evaluated 316 caudal approach epidural steroid injections given by staff radiologists and residents over a 1-year period and noted that of 111 procedures performed by physicians who had given fewer than 10 epidural steroid injections, 53 (47.7%) resulted in correct nonfluoroscopically-directed placement of the needle.20 For physicians who had performed between 10 and 50 such procedures, 62 (53.4%) of 116 had correct nonfluoroscopically-directed placement. For staff physicians, 55 (61.7%) of 89 placements were correct. Even when the sacral hiatus was easily palpated and a staff physician was confident that he or she was within the epidural space, fluoroscopy revealed incorrect placement 14.2% of the time (seven of 49 procedures). In addition, when the needle was positioned within the sacral canal and no blood was evident on Valsalva maneuver or aspiration, the injection was venous in 29 of 316 procedures (9.2%). Price studied 200 consecutive patients referred for an epidural injection and found only 64% of caudal epidural injections were correctly placed (p< 0.001).21 Obesity was associated with a reduced chance of successful placement [odds ratio (OR) 0.34 (95% confidence interval (CI) 0.17 to 0.72) BMI >30 v BMI <30]. Bartynski retrospectively studied 74 lumbar epidural steroid injection (LESI) procedures and found that in only 55 of 74 LESI procedures (74.3%) air pressure resistance was first lost upon appropriately entering the lumbar posterior epidural space.22 Confirmation of tip position was made with nonionic contrast medium injection in an AP and lateral epidurogram. Manchikanti studied 100 consecutive patients and noted successful injection placement without fluoroscopic visualization was confirmed on subsequent	Thank you for your comment. As mentioned above, 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 or in head-to-head trials of transforaminal versus other approaches.

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		fluoroscopic visualization in 77% of patients. 23 However, intravenous placement of the needle was noted in 14% of the patients with positive flashback and aspiration in only half 50% of these patients. Mehta used x-ray monitoring to confirm the accuracy of extradural block in 100 patients who attended the Pain Relief Clinic for treatment of a variety of different conditions.24 Loss of resistance, used to identify entry into the extradural space was then confirmed with contrast injection correct needle placement was noted in only 66 of 87 (79.5%) patients. Collectively this large body of work repeatedly demonstrates that non-image-guided injections are inaccurate. Given the goal of an injection is to deliver an aliquot of medication to a specific target tissue, consideration of nonspecific injections as equal to image-guided injections is inappropriate in modern medicine or in any review of the literature.	
Jeffrey Summers, MD International Spine Intervention Society	Methods	Continued- Of the 29 studies included in the AHRQ report as providing evidence on efficacy of epidural steroid injections vs placebo, there were 15 interlaminar epidural steroid injections, of which only one used fluoroscopic guidance. Of the nine caudal injection studies, only one reported fluoroscopic guidance. Of the five transforaminal epidural steroid injection (TFESI) studies, all utilized fluoroscopic guidance. Therefore, it is worth noting that the body of evidence cited in the AHRQ review, addressing efficacy of epidural steroid injections, involves injection of steroid into an unknown tissue space, with a high probability of never reaching the site of inflammation.	Thank you for your comment. As mentioned above, 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 or in head-to-head trials of transforaminal versus other approaches.
Jeffrey Summers, MD International Spine Intervention Society	Methods	Inappropriate Statistical Analysis The authors also failed to perform an appropriate statistical analysis. The authors clearly state ?In the primary analyses, we combined weighted mean difference (WMD) for pain and standardized mean difference (SMD) for function. The mean difference was calculated using the change between the follow-up and baseline scores.? The use of mean data mandates a normal Gaussian distribution of pain. This would not be present if a treatment resulted in a bimodal distribution of outcomes with responders and non-responders. Also normally distributed data are infrequent in these patient populations given the floor and ceiling effects of a pain scale. This is evident in two studies where mean data failed to show a difference, but the appropriate categorical data showed a difference.6,7 The use of mean data is also not in accordance with the NIH Task Force recommendation for research	We performed analysis on both continuous and dichotomous outcomes, as described in the Methods and presented in the Results. Results were similar with either analysis, though fewer trials reported dichotomous outcomes.

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		standards for chronic low back pain.25 While the authors did state they considered binary outcomes, they again only briefly mentioned this in the results and conclusions and instead focused on the invalid mean changes.	
Jeffrey Summers, MD International Spine Intervention Society	Methods	Collectively, these methodological flaws render meaningless this technology assessment's subsequent presentation of results and conclusions. Failure to establish a diagnosis, failure to assure the use of technically sound therapeutic procedures, and failure to appropriately measure outcomes of those procedures is a recipe for disaster both in medical practice and in the interpretation of medical literature. When the technology under assessment is a medical procedure, the assessors should have a firm knowledge of the technical performance of that procedure, and the pathological processes to which it is directed in contemporary practice. This is clearly not present.	The reviewer is summarizing comments that have been presented earlier, that we responded to in detail.
Jeffrey Summers, MD International Spine Intervention Society	Methods	References: 1. 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. 2. Concato, J., Shah, N. & Horwitz, R. I. Randomized, controlled trials, observational studies, and the hierarchy of research designs. NEJM 2000;342:1887?1892. 3. Cyteval, C. et al. Predictive factors of efficacy of periradicular corticosteroid injections for lumbar radiculopathy. AJNR 2006;27:978?982. 4. Amoretti, N. et al. Symptomatic lumbar facet joint cysts treated by CT-guided intracystic and intraarticular steroid injections. Eur. Radiol 2012;22:2836?2840. 5. Kaufmann, T. J. et al. Clinical effectiveness of single lumbar transforaminal epidural steroid injections. Pain Med 2013;14:1126?1133. 6. Ghahreman, A., Ferch, R. & Bogduk, N. The efficacy of transforaminal injection of steroids for the treatment of lumbar radicular pain. Pain Med 2010;11:1149?1168. 7. Kennedy, D. J. 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;15:548?555. 8. Pneumaticos, S. G., Chatziioannou, S. N., Hipp, J. A., Moore, W. H. & Esses, S. I. Low back pain: prediction of short-term outcome of facet joint injection with bone scintigraphy. Radiology 2006;238:693?698. 9. Jarvik, J. G. & Deyo, R. A. Diagnostic Evaluation of Low Back Pain with Emphasis on Imaging. Ann Intern Med 2002;137:586?597. 10. White, A. A. & Gordon, S. L. Synopsis: workshop on idiopathic low-back pain. Spine 1982;7:141?149. 11. Schwarzer, A.C., Aprill, C.N., Derby, R., Fortin, J., Kine, G., Bogduk, N. The prevalence and clinical features of internal disc disruption in patients with chronic low back pain. Spine 1995;19:1878?1881. 12. Manchikanti, L., Singh, V., Pampati, V., Damron, K.S., Barnhill, R.C., Beyer, C., Cash, K.A. Evaluation of the relative contributions of various structures in chronic low back pain. Pain Physician 2001;4:308?316. 13. Schwarzer, A.C., Aprill, C.N., Derby, R., Fortin, J., Kine, G., Bogduk, N. Clinical features of patients with pain stemming from the lumbar zygapophysial joints. Spine 1995;19:1132?1137. 14. Schwarzer, A.C., Wang, S.C., Bogduk, N., McNaught, P.J., Laurent, R. Prevalence and clinical features of lumbar zygapophysial joint pain: a study in an Australian population with chronic low back pain. Annals of the Rheumatic Diseases 1995;54:100?106.? 15. Manchikanti, L., Manchikanti, K.N., Cash, K.A., Singh, V., Giordano, J. Age-related prevalence of facet-joint involvement in chronic neck and low back pain. Pain Physician 2008;11:67-75. 16. Schwarzer, A.C., Aprill, C.N., Bogduk, N. The sacroiliac joint in chronic low back pain. Spine 1995;20:31?37.? 17. Maigne, J.Y., Aivaliklis, A., Pfefer, F. Results of sacroiliac joint double block and value of sacroiliac pain provocation test in 54 patients with low back pain. Spine 1996;21:1889?1892. 18. el-Khoury, G. Y., Ehara, S., Weinstein, J. N., Montgomery, W. J. & Kathol, M. H. Epidural	Thank you for providing references. We reviewed them for inclusion in the report. All were already included or did not meet inclusion criteria.

Commenter	Section	Comment	Response
		steroid injection: a procedure ideally performed with fluoroscopic control. Radiology 1988;168:554?557. 19. Stitz, M. Y. & Sommer, H. M. Accuracy of blind versus fluoroscopically guided caudal epidural injection. Spine 1999;24:1371?1376. 20. Renfrew, D. L. et al. Correct placement of epidural steroid injections: fluoroscopic guidance and contrast administration. AJNR 1991;12:1003?1007. 21. Price, C. M., Rogers, P. D., Prosser, A. S. & Arden, N. K. Comparison of the caudal and lumbar approaches to the epidural space. Ann Rheum Dis 2000;59:879?882. 22. Bartynski, W. S., Grahovac, S. Z. & Rothfus, W. E. 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 2005;26:502?505. 23. Manchikanti, L., Cash, K. A., Pampati, V., McManus, C. D. & Damron, K. S. Evaluation of fluoroscopically guided caudal epidural injections. Pain Physician 2004;7:81?92 (2004). 24. Mehta, M. & Salmon, N. Extradural block. Confirmation of the injection site by X-ray monitoring. Anaesthesia 1985;40:1009?1012. 25. Deyo, R. A. et al. Focus article: report of the NIH Task Force on Research Standards for Chronic Low Back Pain. Eur Spine J 2014;23:2028?2045.	
Jeffrey Summers, MD International Spine Intervention Society	Results	As described above, the report's methodology yields flawed and unsupportable results.	The reviewer is summarizing comments that have been presented earlier, that we responded to in detail.
Jeffrey Summers, MD International Spine Intervention Society	Results	Injection Approach and Evolution of Techniques An important consideration in the assessment of effectiveness of epidural steroid injections is the target specificity of the approach. The failure to adequately address image guidance has been noted. With three distinct approaches (caudal, interlaminar, transforaminal) included in the AHRQ review, it is important to understand that even when confirmed by image guidance the techniques involved in delivering steroid into the epidural space may well have different results. The caudal and interlaminar techniques deliver medication at some distance from the target site; spread to the ventral epidural space, at the interface of the compressive lesion and the affected nerve, can be neither controlled nor guaranteed. Although the comparative effectiveness of the transforaminal approach versus the interlaminar approach was examined in five head to head trials, the authors use only inadequate continuous data in this comparison. Examination of categorical outcomes in three of the studies favored the transforaminal approach over the interlaminar approach.1,2,3 In one trial the dose of corticosteroid used for the interlaminar approach was twice that of the transforaminal injections.4 A fifth trial compared ?periradicular? injections to interlaminar injections.5 It is not known if the ?periradicular? injections provided spread of corticosteroid to the ventral epidural space, necessary for efficacy.6 The flawed methodology and failure to understand the nuances of technique result in the erroneous conclusion that there is no difference in	Thank you for your comment. As noted above, trials were stratified according to the technique used and we also analyzed head-to-head trials. There were no differences in either continuous or dichotomous outcomes. The three trials cited by the reviewer (Ackerman, Gharibo, Thomas) evaluated different dichotomous outcomes (pain and surgery), which the commenter seems to be combining. We also performed an analysis that excluded the trial that used a periradicular technique, which did not change overall conclusions.

Commenter	Section	Comment	Response
		effectiveness between the interlaminar and transforaminal approaches. Rather, the categorical outcomes of controlled trial evidence support the superiority of the transforaminal approach. This is supported by the clinical effectiveness of transforaminal injections documented in large observational studies,7 comparative effectiveness trials,8 and systematic reviews.9	
Jeffrey Summers, MD International Spine Intervention Society	Results	In addition, it is expected that over time with improvements in technique, technology, and growing clinical expertise, there will be changes in outcomes for procedures, which may bear the same generic description. Pooling of evidence from 2014 with that from the 1980s may do a disservice to developing an appreciation of the effectiveness of these procedures as they are currently performed.	As noted above, we performed analyses stratified by the technique used, we also found no effects in an analysis stratified by date of publication.
Jeffrey Summers, MD International Spine Intervention Society	Results	Corticosteroid Formulation The authors briefly examine the two controlled trials comparing corticosteroid formulations delivered by the transforaminal route, but the important clinical context is lost in the failure to examine the totality of the evidence base. The question of the comparative effectiveness, and safety, of particulate versus non-particulate steroid formulations for transforaminal epidural injections has been a critical one for interventional pain physicians, reflected in its centrality in a Food and Drug Administration?s Safe Use Initiative. Particulate steroid formulations have been associated with rare but catastrophic spinal cord infarctions; the non-particulate steroid dexamethasone has not. A comparative effectiveness study8 and a large Mayo Clinic observational trial of >3600 consecutive transforaminal injections with a noninferiority analysis10 showed no difference in clinical effectiveness of particulate and non-particulate steroids in the treatment of radicular pain. The limited discussion completely misses the important clinical context.	Thank you for your comment. The analysis of effectiveness was based on RCTs, as described in the methods. We added a reference to the FDA materials to the Discussion; we reviewed the FDA materials but found no controlled observational studies on harms that met inclusion criteria. We included trials that compared a particulate vs. non-particulate corticosteroid and found no differences in benefits or harms, and also found no clear differences in estimates based on trials of particulate corticosteroids vs. placebo or non-particulate corticosteroids vs. placebo.

Commenter	Section	Comment	Response
Jeffrey Summers, MD International Spine Intervention Society	Results	Quality of Evidence of Effectiveness: Radicular Pain When evaluating the literature on epidural steroid injections for radiculopathy and herniated disc, the authors rated three studies as ?good?.11,12,13 In the case of Iverson, this study design is good, but the investigative treatment is flawed.11 The investigator chose three possible treatments: subcutaneous saline, epidural saline delivered via the caudal route, or epidural saline and steroid delivered via the caudal route. The authors state that these injections were performed using ultrasound guidance. While ultrasound guidance may help ensure that the needle enters the caudal space, it lacks the ability to analyze flow and ensure that the medication is reaching the desired target. It is known that the caudal epidural space is a highly vascular area and venous uptake is frequent. Successful epidural placement is known to occur in only 74-77% of patients without the use of fluoroscopy,14,15 and L5 nerve root filling with this approach is rare.15 Further, the decision to dilute 40 mg of triamcinolone with 29 mL of saline brings into question how much steroid truly reached the target structure. Lastly, while the authors used validated outcome measures, no categorical data are provided thus limiting the usefulness of the outcomes.	The use of ultrasound guidance in the Iversen trial was described in the results; there was also no evidence to suggest that results of the Iversen trial differed from studies that used imaging guidance (or no imaging guidance).
Jeffrey Summers, MD International Spine Intervention Society	Results	The Karppinen study investigates fluoroscopically-guided transforaminal epidural steroid injections compared with epidural saline.12 Authors have questioned the appropriateness of any epidural injection as a placebo.16 Despite this the study did show early improvements with epidural steroids as compared with saline. This study also fails to provide categorical data, which might have demonstrated even more robust effects of treatment in subsets of patients and, indeed, a subsequent subgroup analysis did show that transforaminal epidural steroid injections were significantly effective for patients with contained herniations.17	The Karpinnen trial was included in the analyses. We added the subgroup results to key question 2 (though interestingly, leg pain favored saline injection at six months even in the contained herniation subgroup).
Jeffrey Summers, MD International Spine Intervention Society	Results	The Cohen study of transforaminal steroids compared with transforaminal etanercept and transforaminal saline is fairly well done, though it again raises concerns about a true placebo group.13 In this case the authors chose valid outcome measures, and provide categorical data. At one month the steroid group had better pain scores, better Oswestry Disability Index (ODI) scores, more positive categorical outcomes, and substantially fewer patients requiring surgery. At three and six months the results normalized but the steroid group continued to use less pain medication and were more satisfied with their treatment than the other groups.	The Cohen trial was included in the analyses.

Commenter	Section	Comment	Response
Jeffrey Summers, MD International Spine Intervention Society	Results	Further, when reviewing the ratings of the quality of the literature, inconsistencies exist. For example, while the authors rated the Iverson and Karppinen papers as ?good?, the Ghahreman study, which seems to meet the same criteria as these studies, was given a quality rating of ?fair?.18 In fact, the Ghahreman study used a better technique than Iverson (fluoroscopically-guided injections) and provides categorical data on validated outcome measures.	Thank you for your comment. We agree that it would be more consistent to grade the Ghareman study as "good" (main flaw was lack of blinding) and adjusted the rating accordingly.
Jeffrey Summers, MD International Spine Intervention Society	Results	The Friedly study was also given a ?good? quality rating.19 While this study design was somewhat typical of practice patterns, the investigator included a very heterogeneous group of spine pain patients with radiographic stenosis in which the "active group" received significantly varying, non-standardized doses of steroids with various non-standardized injection techniques. Patients with buttock pain were equated with patients suffering from true radicular pain, while other possible sources of their pain (e.g., facet mediated pain or sacroiliac pain) were not properly identified and excluded in this study. Further, the investigators failed to utilize appropriate outcome measures. The measures selected were validated for back pain; they were not validated for or designed to assess the symptoms of stenosis (claudication). In addition, when reviewing the data, it becomes unclear how many of the patients in this study are being treated for leg pain vs back pain vs claudication. The authors also failed to provide categorical data, which would allow for identification and analysis of subgroups of patients who respond better than others, as there were global improvements in pain and function with both epidural saline and epidural steroids.	The techniques, doses, and selection methods for Friedly are described in the Results and Table. It enrolled patients with symptoms of neurogenic claudication and imaging findings of spinal stenosis. To clarify, it did report short-term categorical outcomes for pain and function which were included in our analyses. The measures for pain and function were similar to the measures reported in other trials of spinal stenosis.

Commenter	Section	Comment	Response
Jeffrey Summers, MD International Spine Intervention Society	Results	The assessment of study quality is therefore questionable. Controlled studies of epidural steroid injections have been included that do not define the pathoanatomic process to be treated, and fail to use techniques which deliver the corticosteroid to the target tissue. Outdated controlled studies have been included. Studies with varying technique have been aggregated as ?epidural steroid injections?. The methodology has prevented examination of important observational trials. These failings result in the unsupported ?result? that ?epidural steroid injections? provide only minimal benefit in the immediate term. There is ample evidence from controlled trials, large observational trials of prospectively collected data, and systematic reviews looking at the entire evidence base, that lumbar transforaminal epidural steroid injections provide significant pain relief and functional recovery in the immediate, short, and intermediate term.1,2,3,6,7,8, 9,10,17,18	Thank you for your comment. The studies were rated for quality (risk of bias) using standardized criteria, as described in the Methods. Trials were rated using criteria from the Cochrane Back Group (Furlan 2009 article published in Spine), in conjunction with the approach in the AHRQ Methods Guide. The characteristics that you describe are not factors related to risk of bias, but rather issues of external validity (e.g., selection of patients and techniques used) and as described earlier are addressed in detail in the report. We do not believe that observational data such as that taken from registries should trump evidence from well-conducted clinical trials. Well-conducted RCTs may be particularly important for evaluating effects on subjective outcomes such as pain, which is more susceptible to placebo effects. Also, as noted earlier, we found no effects in an analysis stratified by date of publication.
Jeffrey Summers, MD International Spine Intervention Society	Results	Quality of Evidence of Effectiveness: Axial Back Pain Similar to the treatment of radicular pain, the treatment of low back pain with a targeted intervention requires an accurate pathoanatomic diagnosis. Structured reviews of the literature on this topic must take this into account when assessing the quality of the literature. Unfortunately, the authors of the AHRQ report ignored this and assessed the effects of facet joint injections on low back pain ? a symptom, not a pathoanatomic diagnosis. Alternatively, current evidence suggests that facet joint injections are highly successful in patients with low back pain and objective radiographic evidence of a specific pathoanatomic diagnosis. For patients with radiographic evidence of either joint synovitis or a facet joint synovial cyst, prospective studies show positive outcomes20,21,22 and demonstrate half or more of these patients can avoid surgery23,24 and maintain good results at long-term followup25,26. Curiously, two of these studies are prospective randomized controlled trials that do not appear in the AHRQ report.21,22	As described in the Results, no trial evaluated the effect of using a diagnostic block to select patients versus not using blocks. We revised the Discussion to note that a trial that compared selection of patients for facet joint radiofrequency denervation according to use of a dual facet block, single block, or no block found no differences in outcomes (this is the only trial we are aware of that has evaluated the effects of facet joint blocks on outcomes of facet joint procedures, but did not meet inclusion criteria because it evaluated radiofrequency denervation rather than a steroid injection. To clarify, reference 21 (Pneumaticos) was included. We added the Ackerman study.
Jeffrey Summers, MD International Spine Intervention Society	Results	References: 1. Ackerman WE, 3rd, Ahmad M. The efficacy of lumbar epidural steroid injections in patients with lumbar disc herniations. Anesth Analg 2007;104:1217-22 2. Thomas E, Cyteval C, Abiad L, et al. Efficacy of transforaminal versus interspinous corticosteroid injectionin discal radiculalgia - a prospective, randomised, double-blind study. Clin Rheumatol 2003;22:299-304. 3. Gharibo CG, Varlotta GP, Rhame EE, et al. Interlaminar versus transforaminal epidural steroids for the treatment of subacute lumbar radicular pain: a randomized, blinded, prospective outcome study. Pain Physician 2011;14:499-511. 4. Rados I, Sakic K, Fingler M, et al. Efficacy of interlaminar vs transforaminal epidural steroid injection for the treatment of chronic unilateral radicular pain: prospective, randomized study. Pain Med 2011;12:1316-21. 5. Kolsi I, Delecrin J, Berthelot JM, et al. Efficacy of nerve root versus interspinous injections of	Thank you for providing references. We reviewed them for inclusion in the report. As noted above, we added the Ackerman 2008 trial to the report. We also added the Karppinen 2001 (Spine, 26; pgs. 2587-2595).

Commenter	Section	Comment	Response
		glucocorticoids in the treatment of disk-related sciatica. A pilot, prospective, randomized, double-blind study. Joint Bone Spine 2000;67:113-8. 6. El-Yahchouchi C, Wald J, Brault J, Geske J, Hagen C, Murthy N, Kaufmann T, Thielen K, Morris J, Diehn F, Amrami K, Carter R, Shelerud R, Maus T. Lumbar transforaminal epidural steroid injections: does immediate post-procedure pain response predict longer term effectiveness? Pain Med 2014;15:921-8. 7. Kaufmann TJ, Geske JR, Murthy NS, Thielen KR, Morris JM, Wald JT, Diehn FE, Amrami KK, Carter RE, Shelerud RA, Gay RE, Maus TP. Clinical effectiveness of single lumbar transforaminal epidural steroid injections. Pain Med 2013;14:1126-33. 8. Kennedy DJ, Plastaras C, Casey E, Visco CJ, Rittenberg JD, Conrad B, Sigler J, Dreyfuss P. 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;15:548-55. 9. 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- 28. 10. El-Yahchouchi C, Geske JR, Carter RE, Diehn FE, Wald JT, Murthy NS, Kaufmann TJ, Thielen KR, Morris JM, Amrami KK, Maus TP. The noninferiority of the nonparticulate steroid dexamethasone vs the particulate steroids betamethasone and triamcinolone in lumbar transforaminal epidural steroid injections. Pain Med 2013; 14:1650-7. 11. Iversen T, Solberg TK, Romner B, et al. Effect of caudal epidural steroid or saline injection in chronic lumbar radiculopathy: multicentre, blinded, randomised controlled trial. BMJ 2011;343:d5278. 12. Karppinen J, Malmivaara A, Kurunlahti M, et al. Periradicular infiltration for sciatica: a randomized controlled trial. Spine 2001;26:1059-67. 13. Cohen SP, White RL, Kurihara C, et al. Epidural steroids, etanercept, or saline in subacute sciatica: a multicenter, randomized trial. Ann Intern Med 2012;156(8):551-9. 14. Stitz MY, Sommer HM. Accuracy of blind versus fluoroscopically guided caudal epidural injection. Spine 1999;24:1371-1376. 15. Manchikanti L, Cash KA, Pampati V, McManus CD, Damron KS. Evaluation of fluoroscopically guided caudal epidural injections. Pain Physician 2004;7:81-92. 16. Bicket MC, Gupta A, Brown CHI, Cohen SP. Epidural injections for spinal pain: a systematic review and meta-analysis evaluating the "control" injections in randomized controlled trials. Anesthesiology 2013;119:907-931. 17. Karppinen J, Ohinmaa A, Malmivaara, A, et al. Cost effectiveness of periradicular infiltration for sciatica: subgroup analysis of a randomized controlled trial. Spine 2001;26:2587-95. 18. 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. 19. 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. 20. Dolan AL, Ryan PJ, Arden NK, et al. The value of SPECT scans in identifying back pain likely to benefit from facet joint injection. Br J Rheumatol 1996;35:1269-1273. 21. Pneumaticos SG, Chatziioannou SN, Hipp JA, et al. Low back pain: prediction of short-term outcome of facet joint injection with bone scintigraphy. Radiology 2006;238:693-698. 22. Ackerman WE 3rd, 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;101:931-934. 23. Martha JF, Swaim B, Wang DA, et al. Outcome of percutaneous rupture of lumbar synovial cysts: a case series of 101 patients. Spine J 2009;9:899-904. 24. Cambron SC, McIntyre JJ, Guerin SJ, et al. Lumbar facet joint synovial cysts: does T2 signal intensity predict outcomes after percutaneous rupture? AJNR Am J Neuroradiol 2013 Aug;348:1661-4. 25. Allen TL, Tatli Y, Lutz GE. Fluoroscopic percutaneous lumbar zygapophyseal joint cyst rupture: a clinical outcome study. Spine J 2009;9:387-95. 26. Amoretti N, Huwart L, Foti P, et al. Symptomatic lumbar facet joint cysts treated by CT-guided intracystic and intra-articular steroid injections. Eur Radiol 2012;22:2836-40.	

Commenter	Section	Comment	Response
Jeffrey Summers, MD International Spine Intervention Society	Discussion / Conclusion	An initial objection to the Conclusions is that all observational studies, regardless of quality and methodology, were excluded. This is a significant error. A well-conducted observational study can yield higher levels of evidence than a small, poorly conducted or methodologically flawed RCT.	Thank you for your comment. We do not believe that observational data such as that taken from registries should trump evidence from well-conducted clinical trials. Well-conducted RCTs may be particularly important for evaluating effects on subjective outcomes such as pain, which is more susceptible to placebo effects.
Jeffrey Summers, MD International Spine Intervention Society	Discussion / Conclusion	Several of the flawed studies included in the review failed to utilize image guidance, which dramatically alters the technical success of the injection and therefore the report's conclusions regarding efficacy. It is well-documented that image guidance dramatically improves the ability to successfully deliver steroids to the anatomical target.1-7 Other studies either inappropriately or inadequately defined the pathology or symptomology for which the injections were being performed. Additionally, as noted in the AHRQ?s Methods Guide for Effectiveness and Comparative Effectiveness Reviews, ?the interpretation of the evidence and the limits of interpretation are important. Equivalence of different treatments for a group of patients on average does not necessarily imply they are equivalent for all individuals. Attempts to explore subgroups for which benefits or harms of specific interventions vary may be needed.?	Thank you for your comment. The reviewer is summarizing comments that have been presented earlier, that we responded to in detail. The evidence indicates no clear differences in effectiveness based on the technique used and there was insufficient evidence to determine whether imaging guidance increases effectiveness. We describe the patient populations and their diagnoses as it is reported in the studies. Key question 2 addresses how patient and other characteristics impact responsiveness to injections; as described, there was insufficient evidence to determine whether the cause of radicular symptoms, duration of symptoms, imaging findings, or other patient factors, or no clear association. In addition, to clarify, we stratified results for patients with radicular pain, non-radicular pain, and spinal stenosis separately.
Jeffrey Summers, MD International Spine Intervention Society	Discussion / Conclusion	The authors of the AHRQ report failed to heed the wisdom of the AHRQ?s established methods, which highlight the importance of identifying and exploring subgroups of patients for which benefits and harms of spinal injections may vary. Patients with radicular pain were not differentiated from those that may have had somatic leg pain from sources other than the lumbar nerve root. Without a requirement for appropriate imaging (MRI, CT) to determine if there is pathology that could involve the associated lumbar nerve root, this distinction cannot be reliably made. Several studies cited in the references did not require imaging correlation to differentiate the possible origins of lower extremity symptoms,8-12 didn't specify the type of imaging used 9-25 or used an imaging modality (plain X-ray) that would not have been able to adequately evaluate disc or lateral recess architecture 26-28 which would be the most common sources of radicular lower extremity pain.	Thank you for your comment. As mentioned earlier, we describe the patient populations and their diagnoses as it is reported in the studies. Key question 2 addresses how patient and other characteristics impact responsiveness to injections; as described, there was insufficient evidence to determine whether the cause of radicular symptoms, duration of symptoms, imaging findings, or other patient factors, or no clear association. To clarify, we specifically evaluated how use of imaging affected results (there was no clear effect).

Commenter	Section	Comment	Response
Jeffrey Summers, MD International Spine Intervention Society	Discussion / Conclusion	When attempting to determine the effectiveness of a given treatment, it is often necessary to examine beyond the mean response within comparative groups to determine if there were respondents within a given treatment population that did experience a clinically significant benefit, even when the averaged mean response appeared equivalent. The trials cited in this report comparing TFESI to ILESI failed to do this.	Thank you for your comment. We evaluated dichotomous outcomes when they were reported; failure to report dichotomous outcomes is a shortcoming of the evidence, not the methods of the report.
Jeffrey Summers, MD International Spine Intervention Society	Discussion / Conclusion	Lastly, given the social implications of this poorly performed assessment and implementation of any recommendations contained within, it is imperative that practitioners and patients alike fully understand the risks and benefits of a particular treatment and other treatment options. Answering questions about the appropriateness of therapy requires consideration of risks, benefits, and costs of treatment, and again according to the tenants of evidence based medicine, must include individual patient level decision-making.29 Spinal corticosteroid injections have been shown to be very safe when done appropriately in large cohorts of over 20,000 consecutive subjects.30,31 Recent studies have also demonstrated reduced overall costs in patients that receive epidural injections for their pain, mainly attributed to a decrease in loss of productivity.32 This is in stark contrast to alternative treatment options for spine pathology. The surgery-sparing effects of epidural steroid injections have been clearly demonstrated by several studies assessing effectiveness of these injections in patients who had been selected from surgical waiting lists.33-39 This outcome represents considerable cost-savings and avoidance of the risks associated with surgery. There were 14,800 opioid related deaths in the United States in 2008.40 More than 103,000 individuals are hospitalized annually in the United States for NSAID-related serious GI complications, with 16,500 NSAID-related deaths occurring each year in the United States among patients with rheumatoid arthritis and osteoarthritis.41	Thank you for your comment. The purpose of the review is to summarize the evidence, not to make clinical or policy recommendations.

Commenter	Section	Comment	Response
Jeffrey Summers, MD International Spine Intervention Society	Discussion / Conclusion	References: 1. El-Khoury G, Ehara S, Weinstein JW, Montgomery WJ, Kathol MH. Epidural steroid injection: a procedure ideally performed with fluoroscopic control. Radiology 1988;168:554-557. 2. Renfrew DL, Moore TE, Kathol MH, el-Khoury GY, Lemke JH, Walker CW. Correct placement of epidural steroid injections: fluoroscopic guidance and contrast administration. AJNR Am J Neuroradiol.1991;12:1003-7. 3. Stitz MY, Sommer HM. Accuracy of blind versus fluoroscopically guided caudal epidural injection. Spine 1999;24:1371-1376. 4. Price CM, Rogers PD, Prosser ASJ, Arden NK. Comparison of the caudal and lumbar approaches to the epidural space. Ann Rheum Dis 2000;59:879-882. 5. Bartynski WS, Grahovac SZ, Rothfus WE. Incorrect needle position during lumbar epidural steroid administration: inaccuracy of loss air pressure resistance and requirement of fluoroscopy and epidurography during needle insertion. AJNR 2005;26:502-505. 6. Manchikanti L, Cash KA, Pampati V, McManus CD, Damron KS. Evaluation of fluoroscopically guided caudal epidural injections. Pain Physician 2004;7:81-92. 7. Mehta M, Salmon N. Extradural block monitoring. Anaesthesia 1985;40:1009-1012. 8. Bush K, Hillier S. A controlled study of caudal epidural injections of triamcinolone plus procaine for the management of intractable sciatica. Spine 1991;16:572-5. 9. Cuckler JM, Bernini PA, Wiesel SW, et al. The use of epidural steroids in the treatment of lumbar radicular pain. A prospective, randomized, double-blind study. J Bone Joint Surg Am 1985;67:63-6. 10. Dilke TF, Burry HC, Grahame R. Extradural corticosteroid injection in management of lumbar nerve root compression. Br Med J 1973;2:635-7. 11. Dashfield AK, Taylor MB, Cleaver JS, et al. Comparison of caudal steroid epidural with targeted steroid placement during spinal endoscopy for chronic sciatica: a prospective, randomized, double-blind trial. 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Commenter	Section	Comment	Response
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North American Spine Society	General Comments	The North American Spine Society (NASS) appreciates the opportunity to comment on the AHRQ draft technology assessment, Pain Management Injection Therapies for Low Back Pain. NASS is a multispecialty medical organization dedicated to fostering the highest quality, evidence-based, ethical spine care by promoting education, research and advocacy. NASS is comprised of more than 8,000 physician and non-physician members from several disciplines, including orthopedic surgery, neurosurgery, physiatry, pain management, neurology, radiology, anesthesiology, research, physical therapy and other spine care professionals. Questions may be submitted to Pam Hayden, Director of Research & Quality Improvement at phayden@spine.org or 630.230.3690.	Thank you for reviewing the document.
North American Spine Society	Methods	METHODS NASS commends the authors for reviewing and synthesizing a large volume of literature. However, as specialists in spine care, we feel compelled to highlight a few points that contribute additional information on this topic with a primary focus on the poor methodology used for the review.	Thank you for your comment. See responses to specific comments below.

Commenter	Section	Comment	Response
North American Spine Society	Methods	Study Selection We understand that in strict adherence to the evidence-based process, randomized controlled trials (RCTs) were considered the highest level of evidence in this project. However, as an organization also deeply dedicated to EBM, we feel it is incumbent upon us to point out that although RCT?s are considered the gold standard in research, there are varying levels at which they are conducted. Including an assessment of the quality of RCTs as well as considering other well-done studies, such as well designed observational studies, is imperative to the evidence-based process. For example, a level I study comparing nitrates to antacids for the treatment of nonspecific ?chest pain? would have little value despite good study design. "Evidence based medicine is not restricted to randomized trials and meta analyses. It involves tracking down the best external evidence with which to answer our clinical questions."1 We understand that these studies are very much a reflection of the quality of the literature base, however, well-designed and implemented studies that provide categorical data, as opposed to means of continuous data, on outcome measures including pain relief, functional outcomes, decreased use of other health care, surgery-sparing effects, and decreased use of opioids are needed to inform health care providers on which patient subgroups a given intervention may be effective. NASS would encourage AHRQ to also consider observational studies. Concato found that "well-designed observational studies (with either a cohort or a case?control design) do not systematically overestimate the magnitude of the effects of treatment as compared with those in randomized, controlled trials on the same topic."2 Concato stated, "The popular belief that only randomized, controlled trials produce trustworthy results and that all observational studies are misleading does a disservice to patient care, clinical investigation, and the education of healthcare professionals.?2 An evidence base comprised of well designed and implemented observational studies on consecutive patients can yield moderate to high quality evidence in accordance with GRADE. Unless multiple high quality RCTs with appropriately selected patients and technically accurate injections are available, observational studies should not be excluded from a comprehensive systematic review. There are multiple, methodologically rigorous studies which included large cohorts of consecutive subjects that offer additional insights into the clinical effectiveness of these injection procedures.	Thank you for your comment. While observational studies can be useful for harms and in certain instances, as is discussed in the AHRQ Methods Guide, they are highly susceptible to confounding and bias have been shown to be misleading in the field of low back pain as well as in many other fields of medicine, particularly when evaluating the effectiveness of interventions based on subjective outcomes. Therefore, well-conducted randomized trials remain the standard for evaluating the effectiveness of interventions. We do not agree that observational studies should take precedence over higher-quality randomized trials. In addition, over 50 trials of injections exist; therefore, we do not agree that trials are lacking in this area. Please also note that a Topic Refinement Document with Key Questions and PICOTS (including restriction to RCTs) was posted for public comment.

Commenter	Section	Comment	Response
North American Spine Society	Methods	Specific to assessment of spinal injection therapies, many high-quality studies are excluded from this review that provide important evidence regarding the use of spinal interventions. For example, prospective observational studies show good short-term and long-term (one-year) outcomes for lumbar transforaminal epidural injections3 and lumbar facet joint injections.4 These findings are supported by very large retrospective studies with high-quality data, such as a Mayo Clinic study involving more than 2,000 subjects.5 These are just a few examples, and many other examples exist. These studies are inappropriately omitted from the AHRQ technology assessment. While the studies just cited involve patients with different low back symptoms, they all share one important feature. The study populations are well defined, not characterized by a symptom, such as back pain or sciatica; they have a radiographically confirmed patho-anatomic diagnosis that is responsible for their symptoms. This is a critical issue in the assessment of any study involving a targeted intervention.	Thank you for your comment. As mentioned earlier, we do not believe that observational data such as that taken from registries should trump evidence from well-conducted clinical trials. Well-conducted RCTs may be particularly important for evaluating effects on subjective outcomes such as pain, which is more susceptible to placebo effects.
North American Spine Society	Methods	In addition, it is imperative to recognize that study methodology is pointless if the procedures being assessed are not performed on appropriately selected patients using accurate 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 and the procedure was not conducted accurately. Stratification of studies by acceptable, technical performance of the procedures is critically important.	Thank you for your comment. As mentioned earlier, we examined the factors mentioned and there were no patterns suggesting that anything affected the results.
North American Spine Society	Methods	Other significant considerations regarding methodology include underlying diagnosis and its natural history, heterogeneity of procedural techniques along with use of imaging, and statistical analysis.	Thank you for your comment. As mentioned earlier, we examined the factors mentioned and there were no patterns suggesting that anything affected the results.

Commenter	Section	Comment	Response
North American Spine Society	Methods	Diagnostic Specificity Low back and radicular pain are merely symptoms, not diagnoses. Investigations of targeted injection therapies based on patients with a specific anatomic diagnosis repeatedly demonstrate high success rates for clinically meaningful changes in back pain and disability.6,7 Alternatively, spinal injections that treat back pain without a confirmed anatomic diagnosis yield poor results.8 This is an important distinction, however we feel that in this assessment diagnostic etiologies were inappropriately combined throughout the paper. Of the 29 studies comparing epidural steroid injections to placebo, 22 specified radicular pain alone, 6 included a mixture of radicular and back pain, and one study included patients with back pain alone. For perspective, imagine a hypothetical systematic review of prescription medication for the treatment of cough, a symptom. A few studies may show beneficial effects from antibiotics in a group of patients with bacterial pneumonia, a specific diagnosis, whereas pooled data from heterogeneous groups ? 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?	We describe the patient populations and their diagnoses as it is reported in the studies. Key Question 2 addresses how patient and other characteristics impact responsiveness to injections; as described, there was insufficient evidence to determine whether the cause of radicular symptoms, duration of symptoms, imaging findings, or other patient factors, or no clear association. In addition, to clarify, we stratified results for patients with radicular pain, non-radicular pain, and spinal stenosis separately.
North American Spine Society	Methods	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. 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 spinal stenosis, which is less likely to resolve spontaneously with time. Thus short-term relief, as noted by the authors of the AHRQ report, would be very appropriate and expected for 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, as it is likely that 6-12 months following an infection all patients are better regardless of the treatment regimen.	As described in the Methods and presented in the Results, outcomes were analyzed at pre-defined time frames (immediate-term, short-term, intermediate-term, long-term).

Commenter	Section	Comment	Response
North American Spine Society	Methods	The work group?s Key Question #1 illustrates the deficiencies in stratification by diagnosis. This question asks ? In patients with low back pain, what is the effectiveness of ?? This question is based on a symptom that is representative of a variety of diagnostic etiologies. While the authors did state that they considered factors that may present a favorable outcome, they clearly included studies in their analysis that evaluated symptoms rather than diagnoses. In explaining this approach the authors note that: ? In the majority (>85%) of patients with low back pain, symptoms cannot be attributed to a specific disease or spinal pathology.? Their reference for this statement was an article from 20029 that is not the original source of data for this statement, rather it was actually a synopsis of a workshop on idiopathic low back pain from 1982.10 Hence this position, was not supported by original research. In order to be accurate, we reviewed the original article from 1982, and the authors did note that ?estimates of the proportion of all low-back pain that has no definite etiology range widely from about 20% to 85%?. It appears that this is a misquote of a 30 year-old opinion piece. In the same vein, relative to use of inappropriate literature, the assessment appears to rely on a manuscript that predates both modern MRI scanning and the current use of image-guided diagnostic injections, both of which have been repeatedly shown to assist in the diagnosis of spine pathology. Literature from 20-30 years ago was used that merely evaluated a symptom-based population with non-specific techniques including blind injections. While this literature was appropriate and cutting edge at the time of publication, it is not reflective of modern medicine and has introduced flaws in assessment of these procedures.	As noted in the Introduction, the presence of imaging abnormalities is a poor predictor of the presence or severity of low back pain, and there is no reliable reference standard with which to determine the accuracy of "specific" diagnoses for most non-radicular low back pain. In addition, the statement does not apply to radicular back pain, the subject of the majority of trials in this report, which does have specific imaging and clinical findings. We assessed how use of imaging to identify patients with radiculopathy for inclusion impacted results (there were no clear effects).
North American Spine Society	Methods	Advances in Procedural Technology One other concern raised has been the inappropriate grouping of procedural techniques – specifically the use of image guidance. The reliable placement of steroids into the epidural space requires image guidance. The failure rate of ?blind? (non-image guided) needle placement has been studied by several authors. Even in experienced hands, injection of contrast after blind needle placement, demonstrated needle placement during epidural injections was incorrect 25% of the time.11	Thank you for your comment. 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 or in head-to-head trials of transforaminal versus other approaches.
North American Spine Society	Methods	Continued- Stitz determined in a study of 54 consecutive caudal injections without fluoroscopic guidance, successful injection placement on the first attempt occurred in 74.1% of the patients.12 Renfrew also prospectively evaluated 316 caudal approach epidural	Thank you for your comment. As mentioned above, 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 or in head-to-

Commenter	Section	Comment	Response
		steroid injections given by staff radiologists and residents over a one-year period and noted that of 111 procedures performed by physicians who had given fewer than 10 epidural steroid injections, 53 (47.7%) resulted in correct nonfluoroscopically directed placement of the needle.13 For physicians who had performed between 10 and 50 such procedures, 62 (53.4%) of 116 had correct nonfluoroscopically directed placement. For staff physicians, 55 (61.7%) of 89 placements were correct. Even when the sacral hiatus was easily palpated and a staff physician was confident that he or she was within the epidural space, fluoroscopy revealed incorrect placement 14.2% of the time (seven of 49 procedures). In addition, when the needle was positioned within the sacral canal and no blood was evident on Valsalva maneuver or aspiration, the injection was venous in 29 of 316 procedures (9.2%). Price studied 200 consecutive patients referred for an epidural injection and found only 64% of caudal epidural injections were correctly placed ($p< 0.001$).14 Obesity was associated with a reduced chance of successful placement [odds ratio (OR) 0.34 (95% confidence interval (CI) 0.17 to 0.72) BMI >30 v BMI <30]. Bartynski retrospectively studied 74 LESI procedures and found that only 55 of 74 LESI procedures (74.3%), air pressure resistance was first lost upon appropriately entering the lumbar posterior epidural space.15 Confirmation of tip position was made with nonionic contrast medium injection in an AP and lateral epidurogram. Manchikanti studied 100 consecutive patients and noted successful injection placement without fluoroscopic visualization was confirmed on subsequent fluoroscopic visualization in 77% of patients. However, intravenous placement of the needle was noted in 14% of the patients with positive flashback and aspiration in only half 50% of these patients. Mehta used x-ray monitoring to confirm the accuracy of extradural block in 100 patients who attended the Pain Relief Clinic for treatment of a variety of different conditions.16 Loss of resistance, used to identify entry into the extradural space was then confirmed with contrast injection correct needle placement was noted in only 66 of 87 (79.5%) patients. Collectively this large body of work repeatedly demonstrates that non-image guided injections are inaccurate. Given the goal of an injection is to deliver an aliquot of medication to a specific target tissue, a consideration of non-specific injections as equal to image guided injections is inappropriate in modern medicine or in any review of the literature.	head trials of transforaminal versus other approaches.

Commenter	Section	Comment	Response
North American Spine Society	Methods	Continued- Of the 29 studies included in the AHRQ report as providing evidence on efficacy of epidural steroid injections versus placebo, there were 15 interlaminar epidural steroid injections, of which only one used fluoroscopic guidance. Of the 9 caudal injection studies, only one reported fluoroscopic guidance. Of the 5 transforaminal epidural steroid injection (TFESI) studies, all utilized fluoroscopic guidance. Therefore, it is worth noting that the body of evidence cited in the AHRQ review, addressing efficacy of epidural steroid injections, involves injection of steroid into an unknown tissue space, with a high probability of never reaching the site of inflammation.	Thank you for your comment. As mentioned above, 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 or in head-to-head trials of transforaminal versus other approaches.
North American Spine Society	Methods	Statistical Analysis The authors clearly state ?In the primary analyses, we combined weighted mean difference (WMD) for pain and standardized mean difference (SMD) for function. The mean difference was calculated using the change between the follow-up and baseline scores.? The use of mean data mandates a normal Gaussian distribution of pain. This would not be present if a treatment resulted in a bimodal distribution of outcomes with responders and non-responders. Also normally distributed data are infrequent in these patient populations given the floor and ceiling effects of a pain scale. This is evident in two studies where mean data failed to show a difference, but the appropriate categorical data showed a difference.6,7 The use of mean data is also not in accordance with the NIH Task Force recommendation for research standards for chronic low back pain.17 While the authors did state they considered binary outcomes, they again only briefly mentioned this in the results and conclusions and instead focused on the invalid mean changes.	We performed analysis on both continuous and dichotomous outcomes, as described in the Methods and presented in the Results. Results were similar with either analysis, though fewer trials reported dichotomous outcomes.
North American Spine Society	Methods	References 1. 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 312, 71?72 (1996). 2. Concato, J., Shah, N. & Horwitz, R. I. RANDOMIZED, CONTROLLED TRIALS, OBSERVATIONAL STUDIES, AND THE HIERARCHY OF RESEARCH DESIGNS. N. Engl. J. Med. 342, 1887?1892 (2000). 3. Cyteval, C. et al. Predictive factors of efficacy of periradicular corticosteroid injections for lumbar radiculopathy. AJNR Am. J. Neuroradiol. 27, 978?982 (2006). 4. Amoretti, N. et al. Symptomatic lumbar facet joint cysts treated by CT-guided intracystic and intraarticular steroid injections. Eur. Radiol. 22, 2836?2840 (2012). 5. Kaufmann, T. J. et al. Clinical effectiveness of single lumbar transforaminal epidural steroid injections. Pain Med. Malden Mass 14, 1126?1133 (2013). 6. Ghahreman, A., Ferch, R. & Bogduk, N. The efficacy of transforaminal injection of steroids for the treatment of lumbar radicular pain. Pain Med. Malden Mass 11, 1149?1168 (2010). 7. Kennedy, D. J. 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. Malden Mass 15, 548?555 (2014). 8. Pneumaticos, S. G., Chatziioannou, S. N., Hipp, J. A., Moore, W. H. & Esses, S. I. Low back	Thank you for providing references. We reviewed them for inclusion in the report. All were already included or did not meet inclusion criteria.

Commenter	Section	Comment	Response
		pain: prediction of short-term outcome of facet joint injection with bone scintigraphy. Radiology 238, 693?698 (2006). 9. Jarvik, J. G. & Deyo, R. A. Diagnostic Evaluation of Low Back Pain with Emphasis on Imaging. Ann. Intern. Med. 137, 586?597 (2002). 10. White, A. A. & Gordon, S. L. Synopsis: workshop on idiopathic low-back pain. Spine 7, 141?149 (1982). 11. el-Khoury, G. Y., Ehara, S., Weinstein, J. N., Montgomery, W. J. & Kathol, M. H. Epidural steroid injection: a procedure ideally performed with fluoroscopic control. Radiology 168, 554?557 (1988). 12. Stitz, M. Y. & Sommer, H. M. Accuracy of blind versus fluoroscopically guided caudal epidural injection. Spine 24, 1371?1376 (1999). 13. Renfrew, D. L. et al. Correct placement of epidural steroid injections: fluoroscopic guidance and contrast administration. AJNR Am. J. Neuroradiol. 12, 1003?1007 (1991). 14. Price, C. M., Rogers, P. D., Prosser, A. S. & Arden, N. K. Comparison of the caudal and lumbar approaches to the epidural space. Ann. Rheum. Dis. 59, 879?882 (2000). 15. Bartynski, W. S., Grahovac, S. Z. & Rothfus, W. E. 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. 26, 502?505 (2005). 16. Manchikanti, L., Cash, K. A., Pampati, V., McManus, C. D. & Damron, K. S. Evaluation of fluoroscopically guided caudal epidural injections. Pain Physician 7, 81?92 (2004). 17. Deyo, R. A. et al. Focus article: report of the NIH Task Force on Research Standards for Chronic Low Back Pain. Eur. Spine J. Off. Publ. Eur. Spine Soc. Eur. Spinal Deform. Soc. Eur. Sect. Cerv. Spine Res. Soc. 23, 2028?2045 (2014).	
North American Spine Society	Results	RESULTS Injection Approach and Evolution of Techniques Another consideration in the assessment of effectiveness of epidural steroid injections is the target specificity of the approach. With 3 distinct approaches included in the AHRQ review, it is important to understand that even when confirmed by image-guidance, the techniques involved in delivering steroid into the epidural space, may well have different results. It would be beneficial for the technology assessment to further explore differences in approach and the different results that can be expected from them. In addition, it is expected that over time with improvements made in technique and growing clinical expertise, pooling of evidence from 2014 with that from the 1980s may not accurately reflect the effectiveness of these procedures as they are currently performed.	Thank you for your comment. As noted above, trials were stratified according to the technique used and we also analyzed head-to-head trials. There were no differences in either continuous or dichotomous outcomes. The three trials cited by the reviewer (Ackerman, Gharibo, Thomas) evaluated different dichotomous outcomes (pain and surgery), which the commenter seems to be combining. We also performed an analysis that excluded the trial that used a periradicular technique, which did not change overall conclusions. As noted above, we performed analyses stratified by the technique used, we also found no effects in an analysis stratified by date of publication.
North American Spine Society	Results	Evidence of Effectiveness for Radicular Pain When evaluating the literature on epidural steroid injections for radiculopathy and herniated disc, the authors rated 3 studies as ?good.?8,9,10 In the case of Iverson, the study design is good, but the investigative treatment is flawed.8 In this case, the investigator chose three possible treatments: subcutaneous saline, epidural saline delivered via the caudal route, or epidural saline and steroid delivered via the caudal route. The authors state that these injections were performed using ultrasound guidance. While ultrasound guidance may help ensure that the needle enters the caudal space, it lacks the ability to analyze flow and ensure that the medication is reaching the desired	The use of ultrasound guidance in the Iversen trial was described in the results; there was also no evidence to suggest that results of the Iversen trial differed from studies that used imaging guidance (or no imaging guidance).

Commenter	Section	Comment	Response
		target. It is known that the caudal epidural space is a highly vascular area and venous uptake is frequent. Successful epidural placement is known to occur in only 74-77% of patients without the use of fluoroscopy,3,6 and L5 nerve root filling with this approach is rare.6 Further, the decision to dilute 40mg of triamcinolone with 29 mL of saline brings into question how much steroid truly reached the target structure. Lastly while the authors used validated outcome measures, no categorical data are provided thus limiting the usefulness of the outcomes.	
North American Spine Society	Results	The Karppinen study investigates fluoroscopically-guided transforaminal epidural steroid injections compared with epidural saline.9 Authors have questioned the appropriateness of any epidural injection as a placebo.11 Despite this, the study did show early improvements with epidural steroids as compared with saline, but this author also fails to provide categorical data, which might demonstrate even more robust effects of treatment in subsets of patients.	The Karpinnen trial was included in the analyses. We added the subgroup results to key question 2 (though interestingly, leg pain favored saline injection at six months even in the contained herniation subgroup).
North American Spine Society	Results	The Cohen study of transforaminal steroids compared with transforaminal etanercept and transforaminal saline is fairly well done, though it again raises concerns about a true placebo group.10 In this case the author chose valid outcome measures, and provides categorical data. At one month the steroid group had better pain scores, better Oswestry Disability Index (ODI) scores, more positive categorical outcomes and substantially fewer patients requiring surgery. At 3 and 6 months the results normalized, but the steroid group continued to use less pain medication and were more satisfied with their treatment than the other groups.	The Cohen trial was included in the analyses.
North American Spine Society	Results	Furthermore, when reviewing the ratings of the quality of the literature, there seem to be inconsistencies. For example, while the authors rated the Iverson and Karppinen papers as ?good,? the Ghahreman study, which seems to meet the same criteria as these studies, was given a quality rating of ?fair.?12 In fact, the Ghahreman study used a better technique than Iverson (fluoroscopically-guided injections) and provides categorical data on validated outcome measures.	Thank you for your comment. We agree that it would be more consistent to grade the Ghahreman study as "good" (main flaw was lack of blinding) and adjusted the rating accordingly.

Commenter	Section	Comment	Response
North American Spine Society	Results	The Friedly study was also given a ?good? quality rating.13 While this study design was somewhat typical of practice patterns, the investigator included a very heterogeneous group of spine pain patients with radiographic stenosis in which the "active group" received significantly varying, non-standardized doses of steroids with various non-standardized injection techniques. Patients with buttock pain were equated with patients suffering from true radicular pain, while other possible sources of their pain (e.g., facet mediated pain or sacroiliac pain) were not properly identified and excluded in this study. Further, the investigators failed to utilize appropriate outcome measures. The measures selected were validated for back pain, they were not validated for or designed to assess the symptoms of stenosis (claudication). In addition, when reviewing the data, it becomes unclear how many of the patients in this study are being treated for leg pain vs. back pain vs. claudication. The authors also failed to provide categorical data which would allow for identification and analysis of subgroups of patients who respond better than others, as there were global improvements in pain and function with both epidural saline and epidural steroids.	The techniques, doses, and selection methods for Friedly are described in the Results and Table. It enrolled patients with symptoms of neurogenic claudication and imaging findings of spinal stenosis. To clarify, it did report short-term categorical outcomes for pain and function which were included in our analyses. The measures for pain and function were similar to the measures reported in other trials of spinal stenosis.
North American Spine Society	Results	Evidence of Effectiveness for Axial Back Pain Similar to the treatment of radicular pain, the treatment of low back pain with a targeted intervention requires an accurate patho-anatomic diagnosis. Structured reviews of the literature on this topic must take this into account when assessing the quality of the literature. Unfortunately, in this report, assessment was of the effects of facet joint injections on low back pain ? a symptom, not a pathoanatomic diagnosis. Alternatively, current evidence suggests that facet joint injections are highly successful in patients with low back pain and objective radiographic evidence of a specific pathoanatomic diagnosis. For patients with radiographic evidence of either joint synovitis or a facet joint synovial cyst, prospective studies show positive outcomes14,15,16 and demonstrate half or more of these patients can avoid surgery17,18 and maintain good results at long-term follow-up.19.20 Two of these studies are prospective randomized controlled trials that do not appear in the AHRQ report.15,16	As described in the Results, no trial evaluated the effect of using a diagnostic block to select patients versus not using blocks. We revised the Discussion to note that a trial that compared selection of patients for facet joint radiofrequency denervation according to use of a dual facet block, single block, or no block found no differences in outcomes (this is the only trial we are aware of that has evaluated the effects of facet joint blocks on outcomes of facet joint procedures, but did not meet inclusion criteria because it evaluated radiofrequency denervation rather than a steroid injection. To clarify, reference 21 (Pneumaticos) was included. We added the Ackerman study.

Commenter	Section	Comment	Response
North American Spine Society	Results	References: 1. El-Khoury G, Ehara S, Weinstein JW, Montgomery WJ, Kathol MH. Epidural steroid injection: a procedure ideally performed with fluoroscopic control. Radiology 1988;168:554-557. 2. Renfrew DL1, Moore TE, Kathol MH, el-Khoury GY, Lemke JH, Walker CW. Correct placement of epidural steroid injections: fluoroscopic guidance and contrast administration. AJNR Am J Neuroradiol. 1991 Sep-Oct;12(5):1003-7. 3. Stitz MY, Sommer HM. Accuracy of blind versus fluoroscopically guided caudal epidural injection. Spine 1999; 24:1371-1376. 4. Price CM, Rogers PD, Prosser ASJ, Arden NK. Comparison of the caudal and lumbar approaches to the epidural space. Ann Rheum Dis 2000; 59:879-882. 5. Bartynski WS, Grahovac SZ, Rothfus WE. Incorrect needle position during lumbar epidural steroid administration: inaccuracy of loss air pressure resistance and requirement of fluoroscopy and epidurography during needle insertion. AJNR 2005; 26:502-505. 6. Manchikanti L, Cash KA, Pampati V, McManus CD, Damron KS. Evaluation of fluoroscopically guided caudal epidural injections. Pain Physician 2004; 7:81-92. 7. Mehta M, Salmon N. Extradural block monitoring. Anaesthesia 1985; 40:1009-1012. 8. Iversen T, Solberg TK, Romner B, et al. Effect of caudal epidural steroid or saline injection in chronic lumbar radiculopathy: multicentre, blinded, randomised controlled trial. BMJ. 2011;343:d5278. PMID: 21914755. 9. Karppinen J, Malmivaara A, Kurunlahti M, et al. Periradicular infiltration for sciatica: a randomized controlled trial. Spine (Phila Pa 1976). 2001 May 1;26(9):1059-67. PMID: 11337625. 10. Cohen SP, White RL, Kurihara C, et al. Epidural steroids, etanercept, or saline in subacute sciatica: a multicenter, randomized trial. Ann Intern Med. 2012 Apr 17;156(8):551-9. PMID: 22508732. 11. Bicket MC, Gupta A, Brown CHI, Cohen SP. Epidural injections for spinal pain: a systematic review and meta-analysis evaluating the "control" injections in randomized controlled trials. Anesthesiology. 2013;119(4):907-931. PMID 24195874. 12. Ghahreman A, Ferch R, Bogduk N. The efficacy of transforaminal injection of steroids for the treatment of lumbar radicular pain. Pain Med. 2010 Aug;11(8):1149-68. PMID: 20704666. 13. Friedly JL, Comstock BA, Turner JA, et al. A randomized trial of epidural glucocorticoid injections for spinal stenosis. N Engl J Med. 2014 Jul 3;371(1):11-21. PMID: 24988555. 14. Dolan AL, Ryan PJ, Arden NK, et al. The value of SPECT scans in identifying back pain likely to benefit from facet joint injection. Br J Rheumatol, 1996; 35(12), 1269-1273. 15. Pneumaticos SG, Chatziioannou SN, Hipp JA, et al. Low back pain: prediction of short-term outcome of facet joint injection with bone scintigraphy. Radiology, 2006; 238(2), 693-698. 16. Ackerman WE 3rd, 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;101(9), 931-934. 17. Martha JF, Swaim B, Wang DA, et al. Outcome of percutaneous rupture of lumbar synovial cysts: a case series of 101 patients. Spine J. 2009 Nov;9(11):899-904. 18. Cambron SC, McIntyre JJ, Guerin SJ, et al. Lumbar facet joint synovial cysts: does T2 signal intensity predict outcomes after percutaneous rupture? AJNR Am J Neuroradiol. 2013 Aug;34(8):1661-4. 19. Allen TL, Tatli Y, Lutz GE. Fluoroscopic percutaneous lumbar zygapophyseal joint cyst rupture: a clinical outcome study. Spine J. 2009 May;9(5):387-95. 20. Amoretti N, Huwart L, Foti P, et al. Symptomatic lumbar facet joint cysts treated by CT-guided intracystic and intra-articular steroid injections. Eur Radiol. 2012 Dec;22(12):2836-40.	Thank you for providing references. We reviewed them for inclusion in the report. As noted above, we added the Ackerman 2008 trial to the report.
North American Spine Society	Discussion / Conclusion	DISCUSSION/CONCLUSIONS In reviewing the conclusions, NASS is concerned that they are misleading due to flaws in the assessment, as outlined below.	The reviewer is summarizing comments that are presented below, that we responded to in detail.

Commenter	Section	Comment	Response
North American Spine Society	Discussion / Conclusion	In relation to earlier discussions about evidence quality related to RCTs, observational studies, regardless of quality and methodology, were excluded. The quality of RCTs examined is important and not considering other well-done evidence may not allow for as objective of a review process as possible. Study design per se guarantees neither quality nor valid data; the heterogeneity of intra group characteristics, varieties in delivery of care, lack of disease specific standardization of care, and ethical considerations- to name only a few confounders- can all undermine the outcome data despite a rigorous study design. A well conducted controlled trial can yield higher levels of evidence than a small, poorly conducted or methodologically flawed RCT.	Thank you for your comment. We do not believe that observational data such as that taken from registries should trump evidence from well-conducted clinical trials. Well-conducted RCTs may be particularly important for evaluating effects on subjective outcomes such as pain, which is more susceptible to placebo effects. The studies were rated for quality (risk of bias) using standardized criteria, as described in the Methods. Trials were rated using criteria from the Cochrane Back Group (Furlan 2009 article published in Spine), in conjunction with the approach in the AHRQ Methods Guide. The characteristics that you describe are not factors related to risk of bias, but rather issues of external validity and as described earlier are addressed in detail in the report.
North American Spine Society	Discussion / Conclusion	Several studies suffered from a lack of a requirement for image guidance, which could dramatically alter the technical success of the injection and therefore conclusions regarding efficacy. Others either inappropriately or inadequately defined the pathology or symptomology for which the injections were being performed. The lack of image guidance affecting the successful delivery of steroids to the anatomical target is well documented.1-7 As noted in the AHRQ?s Methods Guide for Effectiveness and Comparative Effectiveness Reviews ?the interpretation of the evidence and the limits of interpretation are important. Equivalence of different treatments for a group of patients on average does not necessarily imply they are equivalent for all individuals. Attempts to explore subgroups for which benefits or harms of specific interventions vary may be needed.? Patients with radicular pain were not differentiated from those who may have had somatic leg pain from sources other than the lumbar nerve root. Without a requirement for appropriate imaging (MRI, CT) to determine if there is pathology that could involve the associated lumbar nerve root, this distinction cannot be reliably made. Several studies cited in the references did not require imaging correlation to differentiate the possible origins of lower extremity symptoms,12,16,18,37,38 didn?t specify the type of imaging used 9,10,15,20,23-26,28,29, 39-41 or used an imaging modality (plain X-ray) that would not have been able to adequately evaluate disc or lateral recess architecture8,19,42 which would be the most common sources of radicular lower extremity pain.	The evidence indicates no clear differences in effectiveness based on the technique used and there was insufficient evidence to determine whether imaging guidance increases effectiveness. We describe the patient populations and their diagnoses as it is reported in the studies. Key Question 2 addresses how patient and other characteristics impact responsiveness to injections; as described, there was insufficient evidence to determine whether the cause of radicular symptoms, duration of symptoms, imaging findings, or other patient factors, or no clear association. In addition, to clarify, we stratified results for patients with radicular pain, non-radicular pain, and spinal stenosis separately.

Commenter	Section	Comment	Response
North American Spine Society	Discussion / Conclusion	When attempting to determine the effectiveness of a given treatment, it is often necessary to examine beyond the mean response within comparative groups to determine if there were respondents within a given treatment population that did experience a clinically significant benefit, even when the averaged mean response appear equivalent. The trials cited in this report comparing TFESI to ILESI failed to adequately examine the subgroup populations.	Thank you for your comment. We evaluated dichotomous outcomes when they were reported; failure to report dichotomous outcomes is a shortcoming of the evidence, not the methods of the report.
North American Spine Society	Discussion / Conclusion	Given the impact on patient care, it is imperative that practitioners and patients alike fully understand the risk and benefits of a particular treatment and other treatment options. Answering questions about the appropriateness of therapy requires consideration of risks, benefits, and costs of treatment, and again according to the tenants of evidence based medicine, must include individual patient level decision-making.1 Spinal corticosteroid injections have been shown to be very safe when done appropriately in large cohorts of over 20,000 consecutive subjects.6,7 Recent studies have also demonstrated reduced overall costs in patients that receive epidural injections for their pain, mainly attributed to a decrease in loss of productivity.8 This is in contrast to other treatment options for lumbar spine disorders. There were 14,800 opioid related deaths in the United States in 2008.9 More than 103,000 individuals are hospitalized annually in the United States for NSAID-related serious GI complications, with 16,500 NSAID-related deaths occurring each year in the United States among patients with rheumatoid arthritis and osteoarthritis.10 We agree that injections do not alter spine structural changes that may or may not be associated with pain and functional loss, but they do provide short term relief of symptoms and can reduce the need for surgery in patients with structural changes. However, there are limits to the number of injections over time and certain disorders (axial low back pain without an associated structural change) should not be treated with injections.	Thank you for your comment. The purpose of the review is to summarize the evidence, not to make clinical or policy recommendations.
North American Spine Society	Discussion / Conclusion	NASS thanks the AHRQ for this opportunity to comment and encourages the agency to strongly consider this feedback and the impact it has on the recommendations made.	Noted, thank you for your comments.

Commenter	Section	Comment	Response
North American Spine Society	Discussion / Conclusion	References: 1. El-Khoury G, Ehara S, Weinstein JW, Montgomery WJ, Kathol MH. Epidural steroid injection: a procedure ideally performed with fluoroscopic control. Radiology 1988;168:554-557. 2. Renfrew DL1, Moore TE, Kathol MH, el-Khoury GY, Lemke JH, Walker CW. Correct placement of epidural steroid injections: fluoroscopic guidance and contrast administration. AJNR Am J Neuroradiol. 1991 Sep-Oct;12(5):1003-7. 3. Stitz MY, Sommer HM. Accuracy of blind versus fluoroscopically guided caudal epidural injection. Spine 1999; 24:1371-1376. 4. Price CM, Rogers PD, Prosser ASJ, Arden NK. Comparison of the caudal and lumbar approaches to the epidural space. Ann Rheum Dis 2000; 59:879-882. 5. Bartynski WS, Grahovac SZ, Rothfus WE. Incorrect needle position during lumbar epidural steroid administration: inaccuracy of loss air pressure resistance and requirement of fluoroscopy and epidurography during needle insertion. AJNR 2005; 26:502-505. 6. Manchikanti L, Cash KA, Pampati V, McManus CD, Damron KS. Evaluation of fluoroscopically guided caudal epidural injections. Pain Physician 2004; 7:81-92. 7. Mehta M, Salmon N. Extradural block monitoring. Anaesthesia 1985; 40:1009-1012. 8. Arden NK, Price C, Reading I, et al. A multicentre randomized controlled trial of epidural corticosteroid injections for sciatica: the WEST study. Rheumatology (Oxford). 2005 Nov;44(11):1399- 406. PMID: 16030082. 9. Buchner M, Zeifang F, Brocai DR, et al. Epidural corticosteroid injection in the conservative management of sciatica. Clin Orthop Relat Res. 2000 Jun(375):149-56. PMID: 10853164. 10. Bush K, Hillier S. A controlled study of caudal epidural injections of triamcinolone plus procaine for the management of intractable sciatica. Spine (Phila Pa 1976). 1991 May;16(5):572-5. PMID: 2053000. 11. Buttermann GR. Treatment of lumbar disc herniation: epidural steroid injection compared with discectomy. A prospective, randomized study. 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Commenter	Section	Comment	Response
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Armando Villarreal, MD, MBA John Markman, MD University of Rochester Medical Center Department of Neurosurgery	General Comments	I have read with great interest the report prepared by the Pacific Northwest Evidence based Practice Center (EPC) examining interventional treatments for low back pain, in particular epidural, facet joint, and sacroiliac joint injection. The report fails to achieve its stated purpose of summarizing the current evidence base for these procedures. The analysis would have been strengthened by a patient-centered approach. Unfortunately, there is a pervasive disregard for clinical context. The effectiveness of interventional procedures does not principally depend on the choice of a particular steroid or use of imaging but rather appropriate patient selection. The Food and Drug Administration (FDA) recently convened a meeting to consider the risk benefit profile of epidural corticosteroid injections. Interestingly, the briefing materials prepared by the agency indicate equivalence of corticosteroid efficacy across types and formulations. The agency and its advisory panel favored the use of non-particulate steroid formulations. There was strong consensus that the delivery of particulate	Thank you for the comment. Cervical injections were not within the scope of this review, which focused on lumbar and sacroiliac injections. We did not include case reports of harms because it is not possible to determine comparative risks from them. However, we added a reference to the FDA materials and case reports of serious neurologic harms are already mentioned in the Discussion. However, the FDA materials were not based on a systematic evidence review. Given the low level of evidence available with which to guide selection of corticosteroid and use of imaging guidance, we believe additional research in these areas is warranted, regardless of the findings from the FDA meeting.

Commenter	Section	Comment	Response
		steroids in the cervical region using the transforaminal approach was contraindicated due to the risk of rare but catastrophic neurological injury. Many of these cases were not related to the steroid but rather needle placement (i.e. intravascular, intramedullary sites). That EPC only evaluated large observational studies (>1000 patients) to guage the risk of harm is illustrative of the report's flawed methodology given that the most compelling evidence for the most severe adverse events originates from case reports and closed claim series. The impressive safety record of interlaminar epidural, facet and sacroiliac joint injections was underscored by the exceedingly low rate of serious complications given the high volume of procedures performed daily in the US (~10,000 epidural injections/day). Imaging-guided injections in the spine are used to enhance safety and not solely to improve analgesic benefit. To suggest "additional research would help confirm whether there are difference in outcome associated with different corticosteroids or use of imaging guidance" is to ignore the very safety issues that the FDA so carefully reviewed. Additionally, major pain societies, as well as the American Society of Anesthesiology have clearly indicated that epidural steroid injections should be performed exclusively for radicular pain, again in accordance with EPC findings, which clearly make this conclusion irrelevant.	
Armando Villarreal, MD, MBA John Markman, MD University of Rochester Medical Center Department of Neurosurgery	General Comments	Regarding spinal stenosis, this is an area that requires further investigation, as there are many methodological issues (e.g. definition of study population) that need to be addressed in order to yield finding that are relevant to clinical practice. The recent NEJM study attempts to study three different steroids, at a 3 fold variation in dosing and 2 fold variation in frequency through two different techniques in a single study. This does not meet a face valid standard for an efficacy study given these limitations. Furthermore, local anesthetic is an active comparator (not a placebo control).	As described in the Results, there were no clear differences between local anesthetic injection, saline injection, or non-epidural injection as control interventions; therefore we think it is appropriate to classify all of these as placebo interventions. The design of the Friedly trial are discussed in the Results and shown in the Tables; as there is no consensus on optimal epidural approach or steroid dose (and additional analyses were performed based on the approach used), we do not think there is any reason to discount the findings of the trial.

Commenter	Section	Comment	Response
Armando Villarreal, MD, MBA John Markman, MD University of Rochester Medical Center Department of Neurosurgery	General Comments	Regarding facet injections, the assessment fails to distinguish between interventions with a primary diagnostic rather than therapeutic intent. EPC excluded from their review the therapeutic procedure used for facet-mediated pain (radiofrequency ablation), thus causing a bias of omission on their results.	Radiofrequency denervation was outside the scope of this review, which was determined with input from CMS, key informants, and the public.
Armando Villarreal, MD, MBA John Markman, MD University of Rochester Medical Center Department of Neurosurgery	General Comments	Finally, the analysis uses an overly simplistic chronic low back pain (CLBP) disease construct that glosses over important underlying anatomic and pathophysiologic differences among CLBP patient populations that modulate pain intensity. Importantly, there are no drug therapies available in the United States that are specifically labeled for chronic low back pain. Our best results come from the implementation of a comprehensive approach that utilizes combination analgesia. Interventional pain modalities are one component of such a comprehensive approach.	Thank you for the comment. Most trials did not provide information about co-interventions, but when available it was extracted. There was insufficient evidence to determine how using other interventions impacts effectiveness of injections. The effect of patient characteristics, including methods used to select patients, was addressed in Key Question 2.
Armando Villarreal, MD, MBA John Markman, MD University of Rochester Medical Center Department of Neurosurgery	General Comments	Additional government funding of interventional pain treatments is essential to answer the questions about safety and efficacy this report aims to raise. Unlike, studies of branded opioid medications that use CLBP indications as a model for regulatory approval there is no source of private sector funding for these procedures. Until additional government-funded clinical research support is provided, the best evidence US patients and physicians must rely upon comes from small clinical trials, outcomes registries, case series, and thousands of case reports published in the literature. Unfortunately, the EPC completely ignored these valuable sources of information.	Thank you for the comment. To clarify, randomized trials were included regardless of size, and controlled observational studies on harms were also included. Case reports were excluded because it is not possible to determine comparative risks from them, but they are mentioned in the Discussion.