



Evidence-based Practice Center Systematic Review Protocol

Project Title: *Cervical Degenerative Disease Treatment*

I. Background and Objectives for the Systematic Review

Nature and Burden of Cervical Degenerative Disease

The cervical spine is comprised of seven vertebrae with discs between the vertebrae that are comprised mostly of water. As we age, the vertebral discs become desiccated and lose height, which may cause arthritis to develop (i.e., cervical degenerative disease). Cervical degenerative disease may lead to increased foraminal narrowing (with or without disc herniation) due to increased stress on the vertebral joints, which may cause radiculopathy as nerve roots are pinched. Bony growths along the edges of the vertebral bodies and the posterior longitudinal ligament may cause compression of the spinal cord and associated myelopathy. Both cervical radiculopathy and cervical spondylotic myelopathy can cause pain, sensory deficit and motor deficit. While both conditions can affect the neck and upper extremities, cervical spondylotic myelopathy can also affect the lower extremities, as well as bladder function. Cervical radiculopathy and cervical spondylotic myelopathy may also exist simultaneously.

Although the etiology of cervical degenerative disease is not well understood, it is a common condition that becomes more prevalent with age. The estimated prevalence of any spinal degenerative disease from 2005 to 2017, in people 65 and older, based on Medicare data of approximately 1.7 million individuals, is 27.3%, with the highest prevalence for degenerative disc disease (12.2%).¹ In a separate Medicare database study, 3,156,215 individuals were identified with degenerative cervical disease (incidence 18.9% for females, 13.1% for males between 2006 and 2012).² However, the presence of cervical degenerative disease may not correlate well with symptoms.³ For example, one systematic review⁴ found the prevalence of multilevel degenerative disc pathology to be 64.5% (compared with 89.7% in a symptomatic population).

Management of Cervical Degenerative Disease

Of over 3 million individuals with cervical degenerative disease in the study mentioned above, 32% were treated nonoperatively and 7% were treated with spinal fusion within a year of diagnosis.² Surgical treatment for cervical radiculopathy varies and includes anterior cervical discectomy and posterior cervical foraminotomy. Additionally, intervertebral spacers and additional plating may be used, the vertebrae may or may not be fused, and the cervical disc(s) may or may not be replaced.⁵ In addition to anterior cervical discectomy with fusion and anterior cervical corpectomy with fusion, surgical

treatment for cervical spondylotic myelopathy also includes laminoplasty, laminectomy, and laminectomy with fusion.⁶ Nonoperative treatment of cervical degenerative disease includes analgesics, corticosteroids, neck immobilization, cervical traction, interventional approaches (e.g., radiofrequency ablation), physical therapy, exercises, thermal therapy, and avoidance of provocative activities.^{7,8} The goals of both surgical and nonoperative treatments are to alleviate pain, improve neurologic function, and prevent progression or recurrence. Intraoperative neuromonitoring (e.g., somatosensory, motor evoked potential measurements, spontaneous and triggered electromyography) may improve the safety of cervical spine surgery by providing assessments of neural structures and detecting neurological injury during surgery to potentially mitigate or prevent further injury. Preoperative neuroimaging in cervical myelopathy is used to confirm the clinical diagnosis. Various degenerative features are evident on cervical Magnetic Resonance Imaging (MRI) such as decreased vertebral height, osteophyte formation, disc bulging and whether it is symmetric or asymmetric, hypertrophy and ossification of the posterior longitudinal ligament, spinal cord compression, flattening, and tethering of the spinal cord to spinal canal.⁹ MRI findings can then guide selection of treatment and if intraoperative, the most appropriate surgical approach to treatment.

Decisional Dilemmas and Challenges

In symptomatic cervical degenerative disease quality of life is diminished; function may also be diminished and some deficits may become permanent. Understanding which treatment is likely to result in best outcomes for any patient with cervical degenerative disease is a key decisional dilemma, and will only increase in importance as the US population ages and cervical degenerative disease becomes more prevalent. Other decisional dilemmas to be addressed in this review include: (1) determining which operative or nonoperative treatment(s) for each condition (i.e., cervical radiculopathy, cervical spondylotic myelopathy) is/are most appropriate; (2) determining the optimal surgical approach (e.g., arthroplasty versus anterior discectomy and fusion with 1- or 2-level disease); (3) benefits of intraoperative neuromonitoring (e.g., possible improved intermediate and health outcomes); (4) the optimal use of imaging (e.g., to identify symptomatic pseudarthrosis after cervical fusion); and (5) the possibility of population differences (e.g., based on age, severity of disease, location of degenerative disease). It is expected that there will be trade-offs associated with each intervention (e.g., potential symptomatic improvement and decreased risk of neurological sequelae with surgical treatment, but increased risk of surgical complications).

Challenges and controversies related to this topic include: (1) determining the indications for surgical versus nonsurgical treatments in persons without myelopathy or significant/progressive neurological deficits; (2) lack of large, high-quality randomized trials¹⁰⁻¹² that compare surgical versus nonsurgical approaches, different surgical approaches (e.g., anterior versus posterior approaches such as anterior discectomy and fusion versus posterior cervical foraminotomy; different prostheses for arthroplasty such as low-profile versus standard cages; different graft materials for fusion, such as autogenic bone grafts, allografts, or osteoinductive proteins), or different nonsurgical treatments (e.g., radiofrequency ablation, exercise, physical therapy, heat therapy) with

surgical approaches, including minimally invasive approaches;^{13,14} (3) lack of clarity about the effect of intraoperative neuromonitoring on outcomes in cervical spondylotic myelopathy and whether any benefits of intraoperative neuromonitoring on operative, intermediate outcomes result in improved health outcomes;¹⁵ (4) unclear indications for imaging in preoperative and postoperative settings (e.g., preoperative magnetic resonance imaging in cervical spondylotic myelopathy,^{16,17} postoperative imaging to identify symptomatic pseudarthrosis after cervical fusion surgery);¹⁸ (5) utility of patient characteristics (e.g., age, gender, obesity, bone density, location of degenerative disease [central, paracentral, foraminal], MRI findings, severity of disability, duration of symptoms, number of vertebral levels involved) to guide therapy selection;¹⁹⁻²³ (6) clinical heterogeneity among studies (e.g., different cervical levels affected, different cervical prosthesis used, variability in surgeon experience, variable followup duration, inconsistency in the evaluation of severity of spinal cord disease);^{5,14,24-28} (7) high rate of industry sponsorship,¹² which could influence design, conduct, or reporting of studies; (8) poor reporting of harms, especially long-term harms (e.g., arthroplasty); and (9) determining which outcomes to assess and challenges in assessing them (e.g., use of multiple instruments to measure pain and neurological function) and categorizing the magnitude of effects.

Rationale for Evidence Review

To facilitate resolution of the decisional dilemmas identified above and provide updated evidence for clinical recommendations and shared decision-making, this systematic review will compare the effectiveness and harms of treatments for cervical degenerative disc disease with or without cervical radiculopathy or myelopathy. We will also assess how effectiveness and harms may differ by patient and disease characteristics (e.g., age, gender, severity of disease, vertebral level(s) of involvement). Intended audiences for this review are those seeking to update clinical recommendations as well as other stakeholders including clinicians, policy makers, patients, their caregivers and researchers.

This topic was nominated by the Congress of Neurological Surgeons (CNS), which published prior guidelines on the management of cervical degenerative disease in 2009.²⁹⁻³¹ We will conduct a systematic review that will be broadly useful to clinicians, patients, and policy makers, and will also inform the development of updated guidelines from CNS or others. This review will include nonoperative management of cervical degenerative disease as compared with operative management, which was not part of the previous CNS guidelines.³¹ Additionally, there were several gaps in the evidence identified in the previous CNS guidelines³¹ that we will address with this systematic review (e.g., the development of kyphotic deformity after surgery and its association with health outcomes; the effects of patient age, duration of symptoms, and MRI T2 hyperintensity as prognostic indicators; and the identification of optimal treatment for soft lateral cervical disc displacement causing radiculopathy).

II. The Key Questions

Provisional Key Questions, and description of patients, interventions, comparators, outcomes, timing, settings, and study design (PICOTS), and analytic framework for this topic were posted on the Agency for Healthcare Research and Quality (AHRQ) Website from December 22, 2021, to January 12, 2022. One public commenter from the National Institute of Arthritis and Musculoskeletal and Skin Diseases suggested further exploration of non-operative alternatives (Provisional KQ1), perhaps as a separate KQ, with a focus on pre- and post-operative physical therapy improving outcomes after surgery. The same commenter recommended adding a KQ (after Provisional KQ9) to understand the effectiveness of different interventions to reduce post-surgical pain, including opioids, non-opioid medicines, and other interventions. No other comments were made on the KQs or PICOTs. Based on the comments made during the public posting of the KQs, we added KQ2 to address add-on therapies.

The revised key questions, analytic framework and PICOTS table below incorporate input from Key Informants (KIs) and the public commenter.

Key Questions

The Key Questions (KQs) for this review are as follows*:

KQ1. In patients with radiographic spinal cord compression and no cervical spondylotic myelopathy, what are the comparative effectiveness and harms of surgery compared to non-operative treatment or no treatment?

KQ2. In patients with radiographic spinal cord compression and mild to severe myelopathy, what is the effectiveness and harms of surgery versus non-operative treatment or no treatment? How do the effectiveness and harms vary by level of severity of myelopathy at the time of surgery?

KQ3. In patients with cervical degenerative disease, what are the comparative effectiveness and harms of surgical compared to non-operative treatment?

KQ4. In patients with cervical degenerative disease, what are the comparative effectiveness and harms of therapies added on to surgery (pre- or post-operative) compared with the same surgery alone?

KQ5. In patients with cervical radiculopathy due to cervical degenerative disease, what are the comparative effectiveness and harms of posterior versus anterior surgery?

KQ6. In patients with cervical degenerative disease, what are the comparative effectiveness and harms of posterior versus anterior surgery in patients with greater than or equal to three level disease?

KQ7. In patients with cervical spondylotic myelopathy due to cervical degenerative disease, what are the comparative effectiveness and harms of cervical laminectomy and fusion compared to cervical laminoplasty in patients?

KQ8. In patients with cervical spondylotic radiculopathy or myelopathy at one or two levels, what are the comparative effectiveness and harms of cervical arthroplasty compared to anterior cervical discectomy and fusion?

KQ9. In patients undergoing anterior cervical discectomy and fusion, what are the comparative effectiveness and harms of surgery based on interbody graft material or device type?

KQ10. In patients with pseudarthrosis after prior anterior cervical fusion surgery, what are the comparative effectiveness and harms of posterior approaches compared to revision anterior arthrodesis?

KQ11. In patients with cervical spondylotic myelopathy, what is the prognostic utility of preoperative magnetic resonance imaging (MRI) findings for neurologic recovery after surgery?

KQ12. What is the sensitivity and specificity of imaging assessment for identifying symptomatic pseudarthrosis after prior cervical fusion surgery?

KQ13. In patients with cervical spondylotic myelopathy, what are the comparative effectiveness and harms of intraoperative neuromonitoring (e.g., with somatosensory or motor evoked potential measurements) versus no neuromonitoring on clinical outcomes in patients undergoing surgery?

*For purposes of these key questions, we are focusing on symptomatic cervical degenerative disc disease; with the exception of Key Question 1, evaluation and management of asymptomatic disease is beyond the scope of this review.

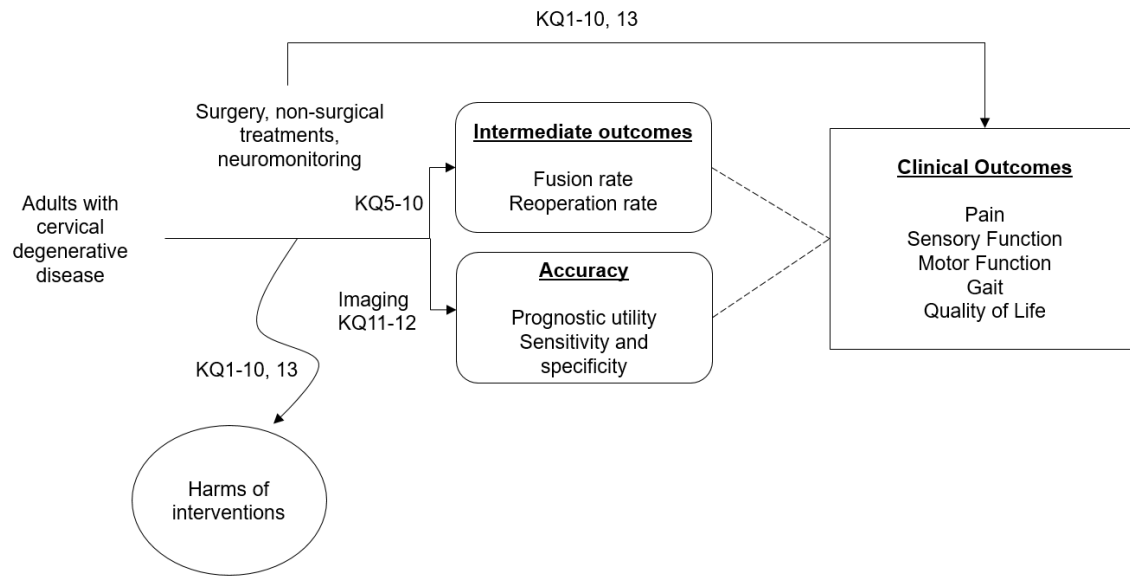
Contextual Questions

CQ1. What is the prevalence of cervical degenerative disease with spinal cord compression in asymptomatic patients?

CQ2. What is the natural history of untreated spinal cord compression in patients with cervical degenerative disease?

III. Analytic Framework

Figure 1. Analytic Framework



KQ = Key Question

IV. Methods

Criteria for Inclusion/Exclusion of Studies in the Review

The criteria for inclusion and exclusion of studies for the systematic review will be based on the Key Questions and the specific criteria listed below in Table 1.

Table 1. PICOTS: Inclusion and exclusion criteria

	Inclusion	Exclusion
Population	<ul style="list-style-type: none"> Age 18 and above with symptomatic cervical degenerative disease (e.g., pain, radiculopathy, myelopathy) for all KQs except for KQ1, which includes asymptomatic patients Effectiveness and harms of surgery based on patient characteristics, disease characteristics and radiographic characteristics (e.g., age, gender, comorbidities [e.g., comorbid lumbar disease, autoimmune disease, neurological disease, mental illness, Down's syndrome], severity of cervical degenerative disease, Frailty Index, sagittal vertical aspect, degree of 	<ul style="list-style-type: none"> Younger than 18 years Patients without cervical degenerative disease Nonhumans

	kyphosis, prior treatment [e.g., bracing, traction, medications, massage, acupuncture, injections, chiropractic care, spinal manipulation], duration of pain, skill of surgeon)	
Intervention	<ul style="list-style-type: none"> • Cervical spine surgery (e.g., discectomy, disc replacement, fusion, arthroplasty, laminectomy, laminoplasty, corpectomy, cervical hybrid surgery, foraminotomy) • Non-surgical treatments (e.g., heat, exercise, acupuncture, drugs, radiofrequency ablation, steroid injections, Botox® for neck pain, psychological strategies [e.g., cognitive behavioral therapy], occupational therapy, multidisciplinary rehabilitation) • Intraoperative neuromonitoring • Imaging to identify symptomatic pseudarthrosis after cervical fusion surgery • Preoperative MRI to predict neurologic recovery in myelopathy 	<ul style="list-style-type: none"> • Preoperative imaging using CT or plain films
Comparators	<ul style="list-style-type: none"> • Any included intervention • Placebo, waitlist, active control 	<ul style="list-style-type: none"> • Nonoperative intervention versus nonoperative intervention without surgical comparator
Outcomes	<ul style="list-style-type: none"> • Pain, sensory function, motor function, gait, quality of life (e.g., VAS, NRS, NDI, SF-36, SF-12, EQ-5Dm, mJOA score, Nurick score, MDI, PROMIS-29, dysphagia scales, return to work) • Fusion rate, reoperation rate • Harms (e.g., withdrawals due to adverse events, serious adverse events, new symptomatic adjacent segment disease, postoperative infection, device failure, ossification of the posterior ligament, development of kyphotic deformity) • Sensitivity and specificity of imaging after cervical fusion surgery 	<ul style="list-style-type: none"> • Nonvalidated instruments
Timing	<ul style="list-style-type: none"> • All time periods 	
Setting	<ul style="list-style-type: none"> • Inpatient, outpatient, ambulatory surgical centers 	

Study Design	<ul style="list-style-type: none"> • RCTs, prospective trials and retrospective observational studies with a control group (study N\geq50), current systematic reviews for identification of additional studies 	<ul style="list-style-type: none"> • Pre-post single-arm studies, case series, case reports, systematic reviews published prior to 2007
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CT = computed tomography; EQ-5D = EuroQol-5 dimension instrument; KQ = key question; MDI = myelopathy disability index; MRI = magnetic resonance imaging; mJOA = modified Japanese orthopedic association scale; NDI = neck disability index; NRS = numerical pain rating scale; PROMIS-29 = patient reported outcome measurement information system; RCT = randomized controlled trial; QOL = quality of life; SF = short form health survey (12 or 36 items); VAS = visual analogue scale for pain.

Study Designs: Randomized controlled trials (RCTs) will be included for all key questions. In the absence of evidence from RCTs, we will include prospective, comparative trials. Nonrandomized, controlled studies of interventions will also be considered for harms.

Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

Publication Date Range: For key questions that compare operative approaches, we will search databases for studies published after 2006 (studies published in 2007 or earlier were included in the 2009 guidelines).³¹ Additionally, we will review all studies included in the 2009 guidelines for inclusion in this review.³¹ For key questions not covered by the 2009 guidelines³¹ (e.g., operative versus nonoperative studies, neuromonitoring studies) we will search the databases from 1980 to the present in order to identify relevant, earlier studies based on when technologies such as neuromonitoring and advanced imaging were first used in research trials. Electronic literature searches will be updated while the draft report is posted for public comment and peer review to capture any new publications. Literature identified during the updated search will be assessed using the same process of dual review as all other studies considered for inclusion in the report. If any pertinent new literature is identified for inclusion in the report, it will be incorporated before the submission of the final report.

Literature Databases: Ovid® MEDLINE®, EMBASE®, and the Cochrane Library will be searched. Appendix A contains our sample MEDLINE® search strategy which will be adapted to search the other databases.

Hand Searching: Reference lists of included articles and relevant systematic reviews will also be searched for includable literature.

Process for Selecting Studies

In accordance with the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*,³² we will use the pre-established criteria above to screen citations (titles and abstracts) identified through our searches to determine eligibility for full-text review. We will prioritize evidence from RCTs. In the absence of evidence from RCTs, we will prioritize prospective, comparative evidence from nonrandomized studies that control for

potential confounding. We will focus on primary studies and review systematic review references for relevant studies as it is unlikely that SRs will fully answer the key questions. All excluded abstracts will be dual reviewed to assure accuracy for inclusion. All citations deemed appropriate for inclusion by at least one reviewer will be retrieved. Each full-text article will be independently reviewed for eligibility by two team members, including any articles suggested by Technical Expert Panel (TEP) members, peer reviewers or that arise from the public posting process. Any disagreements will be resolved by consensus. A record of studies excluded at the full-text level with reasons for exclusion will be maintained.

Data Abstraction and Data Management

To capture information related to intervention heterogeneity and complexity and heterogeneity across enrolled populations, we will create tailored detailed data abstraction tools for each key question. Using standardized templates, data from included studies will be abstracted into categories that include but are not limited to: study design, setting, country, funding, sample size, eligibility criteria, attrition, population and clinical characteristics including key subgroups (e.g., age, gender, obesity, number of vertebral levels involved, severity of radiculopathy and/or myelopathy), effectiveness-related outcomes (e.g., validated pain, function and quality of life measures), as well as treatment-related side effects/harms. Information on potential confounders and methods of adjustment will also be abstracted as will data on followup. Information relevant for assessing applicability will be abstracted, including the characteristics of the population, interventions and the number of patients enrolled relative to the number assessed for eligibility. All extracted study data will be verified for accuracy and completeness by a second team member.

Assessment of Methodological Risk of Bias of Individual Studies

We will use predefined criteria to assess the risk of bias of included studies. Randomized trials will be evaluated using criteria and methods developed by the Cochrane Back Review Group.³³ Nonrandomized, comparative studies will be evaluated using criteria developed by the U.S. Preventive Services Task Force³⁴ and will include methods of patient selection (e.g., consecutive patients, use of an inception cohort) and appropriate control for confounding of relevant prognostic factors. We will downgrade studies that do not provide randomization, allocation, and/or blinding details, have a high rate of study loss to followup, or demonstrate selective reporting or other bias accordingly. To address the potential for publication bias, we will conduct appropriate statistical tests (e.g., funnel plots, statistical tests for Egger's small sample effects) when we have sufficient (≥ 10) studies.³⁵ These criteria and methods will be used in concordance with the approach recommended in the chapter, *Assessing the Risk of Bias of Individual Studies When Comparing Medical Interventions*,³⁶ from the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.³² Studies will be rated as being "low," "moderate," or "high" risk of bias as described below in Table 2.

Table 2. Criteria for grading the risk of bias of individual studies

Rating	Description and Criteria
Low	<ul style="list-style-type: none">• Least risk of bias, results generally considered valid• Employ valid methods for selection, inclusion, and allocation of patients to treatment; report similar baseline characteristics in different treatment groups; clearly describe attrition and have low attrition; use appropriate means for preventing bias (e.g., blinding of patients, care providers, and outcomes assessors); and use appropriate analytic methods (e.g., intention-to-treat analysis)
Moderate	<ul style="list-style-type: none">• Susceptible to some bias but not enough to necessarily invalidate results• May not meet all criteria for low risk of bias, but no flaw is likely to cause major bias; the study may be missing information making it difficult to assess limitations and potential problems• Category is broad; studies with this rating will vary in strengths and weaknesses; some studies rated moderate risk of bias are likely to be valid, while others may be only possibly valid
High	<ul style="list-style-type: none">• Significant flaws that imply biases of various kinds that may invalidate results; “fatal flaws” in design, analysis or reporting; large amounts of missing information; discrepancies in reporting; or serious problems with intervention delivery• Studies are at least as likely to reflect flaws in the study design or execution as the true difference between the compared interventions• Considered to be less reliable than studies rated moderate or low risk of bias when synthesizing the evidence, particularly if discrepancies between studies are present

Each study evaluated will be dual reviewed for risk of bias by two team members. Any disagreements will be resolved by discussion and consensus.

Data Synthesis

We will conduct meta-analyses of randomized trials and nonrandomized studies separately and report them separately unless findings are very consistent across study designs and the studies are clinically homogeneous. When appropriate, we will conduct a sensitivity analysis removing studies rated high risk of bias to determine the effect size and direction of the evidence with only studies rated as moderate or low risk of bias. Findings will be synthesized qualitatively (e.g., ranges and descriptive analysis, with interpretation of results) and quantitatively (meta-analysis) when appropriate. To address anticipated heterogeneity in reported outcomes, variation in their definitions and criteria for what constitutes response, we will focus on validated outcomes for pain, function and quality of life. We will classify the magnitude of effects for continuous measures of pain and function using a similar system as in prior AHRQ reviews on pain³⁷⁻⁴¹ (Table 3) and will evaluate the proportion of patients meeting thresholds for clinically important differences (e.g., >30% pain relief) when reported. For analysis of continuous measures

across the same outcome measures (e.g., VAS for pain) we will report mean differences and use standardized mean differences for outcomes measures with similar constructs together with 95% confidence intervals.

Table 3. Definition of effect sizes

Effect Size	Definition
Small effect	<ul style="list-style-type: none"> • MD 0.5 to 1.0 points on a 0 to 10-point scale, 5 to 10 points on a 0 to 100-point scale • SMD 0.2 to 0.5 • RR/OR 1.2 to 1.4
Moderate effect	<ul style="list-style-type: none"> • MD >1 to 2 points on a 0 to 10-point scale, >10 to 20 points on a 0 to 100-point scale • SMD >0.5 to 0.8 • RR/OR 1.5 to 1.9
Large effect	<ul style="list-style-type: none"> • MD >2 points on a 0 to 10-point scale, >20 points on a 0 to 100-point scale • SMD >0.8 • RR/OR ≥ 2.0

MD = mean difference; OR = odds ratio; RR = relative risk; SMD = standardized mean difference

We will consider pooling studies if there are at least two clinically and methodologically comparable studies.^{42,43} Meta-analyses, using profile-likelihood random effect models will be conducted to summarize data and obtain more precise estimates. For nonrandomized studies, pooled estimates will be based on author-reported effect estimates that adjust for key confounders. Sensitivity and subgroup analyses will be performed to explore statistical heterogeneity using the I^2 statistic and differences by study risk of bias, study design, intervention differences, patient characteristics (e.g., age, gender, severity of disease), and outcome measurements as data permit. If outcomes are reported at different timepoints postoperatively (e.g., 1 month, 12 months, 48 months), we will stratify analyses by duration of followup, data permitting. We will summarize within-study analyses of subgroup differences and perform study-level analyses on key demographic, intervention, and clinical factors as data permit in attempt to evaluate differential effectiveness and harms. Applicability to U.S. practice settings will be assessed based on the Evidence-based Practice Center (EPC) Methods Guide, using the PICOTS framework.⁴⁴ See section on Applicability below.

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

Outcomes to be assessed for strength of evidence will be prioritized based on input from the Technical Expert Panel. Based on this prioritized list, the strength of evidence for comparison-outcome pairs within each KQ will be initially assessed by one researcher for each clinical outcome (see PICOTS) by using the approach described in the *Methods Guide for Effectiveness and Comparative Effectiveness Review*.³² To ensure consistency and validity of the evaluation, the initial assessment will be independently reviewed by at least one other experienced investigator using the following criteria:

- Study limitations (low, medium, or high level of study limitations)

- This is the degree to which studies for a given outcome are likely to have reduced bias based on study design, analysis, and conduct. The aggregate risk of bias across individual studies reporting an outcome is considered.
- Consistency (consistent, inconsistent, or unknown/not applicable)
 - This is the degree to which studies report similar magnitudes of effect (i.e., range sizes are similar) or same direction of effect (i.e., effect sizes have the same sign)
- Directness (direct or indirect)
 - This is degree to which the outcome is directly or indirectly related to health outcomes of interest. Patient centered outcomes are considered direct
- Precision (precise or imprecise)
 - Describes the level of certainty of the effect estimate for a particular outcome with a precise estimate being one that allows a clinically useful conclusion. This may be based on sample size sufficiency and number of events. If these are adequate, the interpretation of the confidence interval is also considered. When quantitative synthesis is not possible, sample size and assessment of variance within individual studies will be considered.
- Reporting bias (suspected or undetected)
 - Publication bias, selective outcome reporting, and selective analysis reporting are types of reporting bias. If sufficient numbers of RCTs (≥ 10) are available, quantitative funnel plot analysis may be done.

The strength of evidence will be assigned an overall grade of high, moderate, low, or insufficient according to a four-level scale (Table 4) by evaluating and weighing the combined results of the above domains.

Table 4. Description of the strength of evidence grades

Strength of Evidence	Description
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.

Strength of Evidence	Description
Insufficient	We are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. The body of evidence has unacceptable deficiencies which precludes reaching a firm conclusion. If no evidence is available, it will be noted as “no evidence”

The strength of the evidence may be downgraded based on the limitations described above. There are also situations where the observational evidence may be upgraded (e.g., large magnitude of effect, presence of dose-response relationship or existence of plausible unmeasured confounders), if there are no downgrades on the primary domains, as described in the AHRQ Methods Guide.^{32,36} Where both RCTs and observational studies are included for a given intervention-outcome pair, we follow the additional guidance on weighting RCTs over observational studies, assessing consistency across the two bodies of evidence, and determining a final rating.³²

Summary tables will include ratings for individual strength of evidence domains (risk of bias, consistency, precision, directness) based on the totality of underlying evidence identified.

Assessing Applicability

Applicability will be assessed in accordance with the AHRQ’s Methods Guide,³² using the PICOTS framework. Applicability refers to the degree to which study participants are similar to real-world patients receiving care for cervical degenerative disease. If patient, clinical, and intervention characteristics are similar, then it is expected that outcomes associated with the intervention for study participants will likely be similar to outcomes in real-world patients. For example, exclusion of participants with psychiatric comorbidities reduces applicability to clinical practice since many patients with chronic pain have such comorbidities, and may respond more poorly to treatment. Multiple factors identified *a priori* that are likely to impact applicability include characteristics of enrolled patient populations (e.g., gender, age, functional status, comorbidities), clinical characteristics (e.g., severity of disease, number of vertebral levels involved, radiographic findings), intervention factors (e.g., intensity and frequency of monitoring, use of co-interventions), outcomes (e.g., use of unvalidated or nonstandardized outcomes), and settings (e.g., clinical setting, country). Review of abstracted information on these factors will be used to assess situations for which the evidence is most relevant and to evaluate applicability to real-world clinical practice in typical U.S. settings. We will provide a qualitative summary of our assessment.

V. Definition of Terms

- Cervical degenerative disc disease: age-related changes in the cervical spine that may result in pain, radiculopathy, and/or myelopathy
- Cervical disc arthroplasty: cervical artificial disc replacement

- Cervical hybrid surgery: use of anterior cervical fusion and anterior disc replacement at different spinal levels in patients with multi-level cervical disc disease
- Corpectomy: removal of vertebral body
- Discectomy: removal of disc
- Foraminotomy: surgery to widen the bony area where spinal nerve roots exit the spinal column
- Fusion: a stabilizing surgery where vertebral levels are fused (via bridging bone) using a bone graft or other material
- Kyphotic deformity: an abnormally forward pitch of the spine, often due to compression of vertebrae
- Laminoplasty: surgical procedure that enlarges the spinal canal by lifting a piece of bone (called the lamina) covering the spinal canal
- Laminotomy: surgical removal of a piece of bone (called the lamina) to enlarge the spinal canal
- Myelopathy: compression of the spinal cord that may result in pain, paresthesias, and reduced functioning
- Pseudarthrosis: failure of fusion after vertebral fusion surgery
- Radiculopathy: caused by a compressed nerve root that may result in pain, paresthesias, and reduced functioning

VI. Summary of Protocol Amendments

None

VII. Review of Key Questions

The Agency for Healthcare Research and Quality (AHRQ) will post the Key Questions for on the AHRQ Effective Health Care Website for public comment. The Evidence-based Practice Center (EPC) will refine and finalize the Key Questions after review of the public comments, and input from Key Informants and the Technical Expert Panel (TEP). All input is intended to ensure that the key questions are specific and relevant.

VIII. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC will solicit input from Key Informants when developing questions for the systematic review. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism. Key Informants must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The AHRQ Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

IX. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and suggest approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism. Technical Experts must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The AHRQ TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified. TEP input will be sought to hone and re-affirm methods in the draft protocol, including perspectives on proposed KQ and PICOTS changes and managing challenges and reporting to enhance usability and inform meaningful presentation of the report.

X. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$5,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XI. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than \$1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than \$1,000 will usually disqualify EPC core team investigators.

XII. Role of the Funder

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XIII. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).

XIV. References

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Appendix A. Sample Search Strategies: Cervical Degenerative Disease Treatment

Strategies will be adapted for databases to be searched.

Patients

("spinal cord diseases"[MeSH Terms] OR ("cervical"[Title/Abstract] AND ("degenerative disease"[Title/Abstract] OR "radiculopathy"[Title/Abstract] OR "myelopathy"[Title/Abstract]))) AND ((humans[Filter]) AND (english[Filter]) AND (alladult[Filter]))

Surgery Key Questions 1,2,3,4,7,8,9

"surgery"[MeSH Subheading] OR "surgical procedures, operative"[MeSH Terms] OR "surgical procedures, operative"[MeSH Terms] OR "general surgery"[MeSH Terms] OR "surgery"[Title] OR "surgical"[Title]

Laminectomy or laminoplasty Key Question 6

"laminectomy"[MeSH Terms] OR "laminoplasty"[MeSH Terms] OR "laminectomy"[Title/Abstract] OR "laminoplasty"[Title/Abstract]

Arthroplasty or discectomy Key Question 7

"arthroplasty"[MeSH Terms] OR "discectomy"[MeSH Terms] OR "arthroplasty"[Title/Abstract] OR "discectomy"[Title/Abstract] OR "discectomy"[Title/Abstract]

Magnetic Resonance Imaging Key Question 10

"Magnetic Resonance Imaging"[MeSH Terms] OR "Magnetic Resonance Imaging"[Title] OR "MRI"[Title]

Diagnostic Imaging Key Question 11

("pseudarthrosis"[MeSH Terms] OR "pseudarthrosis"[Title/Abstract]) AND ("imaging"[Title] OR "diagnostic imaging"[MeSH Terms])

Intraoperative neuromonitoring Key Question 12

"monitoring, intraoperative"[MeSH Terms] OR ("intraoperative"[Title] AND ("monitoring"[Title] OR "neuromonitoring"[Title]))

Reviews (sensitive)

Review (Standard filter)

Systematic Reviews (specific)

Systematic Reviews (Standard filter)

RCT hedge (sensitive)

((((((((groups[tiab])) OR (trial[tiab])) OR (randomly[tiab])) OR (drug therapy[sh])) OR (placebo[tiab])) OR (randomized[tiab])) OR (controlled clinical trial[pt])) OR (randomized controlled trial[pt]))

Clinical Trials (specific)

Clinical Trial (Standard filter)

Observational hedge (sensitive)

(((((("Cohort Studies"[Mesh]) OR "Controlled Clinical Trial"[Publication Type]) OR "Case-Control Studies"[Mesh])) OR (("Evaluation Studies"[Publication Type]) OR "Comparative Study"[Publication Type])) OR (("Comparative Study"[Publication Type]) OR "Follow-Up Studies"[Mesh]))

Observational study type (specific)

"Observational Study" [Publication Type]