BlueCross BlueShield of Alabama

Name of Policy:
Spinal Cord Stimulation

Policy #: 328
Category: Surgery

Latest Review Date: May 2018
Policy Grade: B

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

Spinal cord stimulation (SCS) delivers low voltage electrical stimulation to the dorsal columns of the spinal cord to block the sensation of pain. Spinal cord stimulation devices have a radiofrequency receiver that is surgically implanted and a power source (battery) that is either implanted or worn externally. Other neurostimulators target the dorsal root ganglion (DRG).

Chronic Pain

Spinal cord stimulation (SCS) has been used in a wide variety of chronic refractory pain conditions, including pain associated with cancer, failed back pain syndromes, arachnoiditis, and complex regional pain syndrome (i.e., chronic reflex sympathetic dystrophy). There has also been interest in SCS as a treatment of critical limb ischemia, primarily in patients who are poor candidates for revascularization and in patients with refractory chest pain.

Spinal Cord Stimulation

Spinal cord stimulation (SCS; also referred to as dorsal column stimulation) involves the use of low-level epidural electrical stimulation of the spinal cord dorsal columns. The neurophysiology of pain relief after SCS is uncertain but may be related to either activation of an inhibitory system or blockage of facilitative circuits. SCS has been used in a wide variety of chronic refractory pain conditions, including pain associated with cancer, failed back pain syndromes, arachnoiditis, and complex regional pain syndrome (i.e., chronic reflex sympathetic dystrophy). There has also been interest in SCS as a treatment of critical limb ischemia, primarily in patients who are poor candidates for revascularization and in patients with refractory chest pain.

Spinal cord stimulation devices consist of several components: 1) the lead that delivers the electrical stimulation to the spinal cord; 2) an extension wire that conducts the electrical stimulation from the power source to the lead, and 3) a power source that generates the electrical stimulation. The lead may incorporate from 4 to 8 electrodes, with 8 electrodes more commonly used for complex pain patterns, such as bilateral pain or pain extending from the limbs to the trunk. There are 2 basic types of power source. In one type, the power source (battery) can be surgically implanted. The other, a radiofrequency receiver, is implanted, and the power source is worn externally with an antenna over the receiver. Totally implantable systems are most commonly used.

The patient's pain distribution pattern dictates at what level in the spinal cord the stimulation lead is placed. The pain pattern may influence the type of device used; for example, a lead with 8 electrodes may be selected for those with complex pain patterns or bilateral pain. Implantation of the spinal cord stimulator is typically a two-step process. Initially, the electrode is temporarily implanted in the epidural space, allowing a trial period of stimulation. Once treatment effectiveness is confirmed (defined as at least 50% reduction in pain), the electrodes and radio-receiver/transducer are permanently implanted. Successful spinal cord stimulation may require extensive programming of the neurostimulators to identify the optimal electrode combinations and stimulation channels.

Traditional SCS devices use electrical stimulation with a frequency on the order of 100 to 1000 Hz. In 2015, an SCS device, using a higher frequency (10,000 Hz) than predicate devices was

approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process. High-frequency stimulation is proposed to be associated with fewer paresthesias, which are a recognized effect of SCS. In addition, in 2016, FDA approved a clinician programmer "app" that allows an SCS device to provide stimulation in "bursts" rather than at a constant rate. Burst stimulation is proposed to relieve pain with fewer paresthesias. The burst stimulation device works in conjunction with standard SCS devices. With the newly approved app, stimulation is provided in five 500-Hz burst spikes at a rate of 40 Hz, with a pulse width of 1 ms.

Outcome Measures

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group has provided recommendations for 4 core chronic pain outcome domains that should be included when selecting outcome measures for clinical trials of treatments for chronic pain: (1) pain intensity; (2) physical functioning; (3) emotional functioning; and (4) participant ratings of overall improvement. IMMPACT has also suggested specific outcome measures to address these core domains and has proposed provisional benchmarks for identifying clinically important changes in these specific outcome measures (see Table 1).

Table 1. Health Outcome Measures Relevant to Trials of Chronic Pain

Domain	Outcome Measure	Description	Clinically Meaningful Difference
Pain intensity			
	• Numeric rating scale • Verbal rating scale • Visual analog scale	Rating of pain intensity on a scale of 0 (no pain) to 10 (pain as bad as you can imagine) or from 0 to 10 cm	• Minimally important: 10%-20% decrease • Moderately important: ≥30% decrease • Substantial: ≥50% decrease
Physical functioning			
	Disease specific	Measures of the interference of pain with physical functioning	
	• Multidimensional Pain Inventory Interference Scale	• 60 items, self-report • 12 subscales: interference, support, pain severity, self-control, negative mood, punishing responses, solicitous responses, distracting responses, household chores, outdoor work, activities away from home, and social activities • Items rated on 0- to 6-point scale • Interference subscale score calculated by mean of subscale items	• ≥0.6-point decrease
	• Brief Pain Inventory • Interference Scale	• 7 items, self-report • Measures intensity, quality, relief and interference of pain and patients' ideas of the causes of pain • Mean of the 7 interference items can be used as a measure of pain interference	• 1-point decrease
	• Oswestry Disability Index	Measures functional impairment due to lower back pain: • 10 sections, self-report • Sections: intensity of pain, lifting, ability to care for	• 10 points

Domain	Outcome Measure	Description	Clinically Meaningful Difference
		oneself, ability to walk, ability to sit, sexual function, ability to stand, social life, sleep quality, and ability to travel • Each section is scored on a 0 to 5 scale with 5 indicating the greatest disability • Total score calculated by taking the mean of the section scores and multiplying by 100	
	General	Generic measure of physical functioning	
	• 36-Item Short Form Health Survey	Measure overall health status: • 36 items, self-report • 8 domains: physical function, physical role, general health, bodily pain, mental health, social function, vitality/fatigue, and emotional role • Physical Component Summary and Mental Component Summary scores are aggregate scores that can be calculated • Higher scores indicate better health status	• 5-10 point
Emotional functioning			
	• Beck Depression Inventory	• 21 items, self-report • Measures severity of current symptoms of depressive disorders • Scores range from 0 to 63	• ≥5-point decrease
	• Profile of Mood States	• 65 items, self-report • Measures total mood disturbance with 6 subscales: tension, depression, anger, vigor, fatigue, and confusion • Scores range from 0 to 200	• ≥10- to 15-point decrease
Global rating of improvement			
	• Patient Global Impression of Change	• Single-item, self-rating • 7-point scale ranging from 1 (very much worse) to 7 (very much improved)	• Minimally important: minimally improved • Moderately important: much improved • Substantial: very much improve

Policy:

Effective for dates of service on or after September 29, 2016:

Spinal cord stimulation meets Blue Cross and Blue Shield Alabama's medical criteria for coverage for the treatment of **severe and chronic pain of the trunk or limbs** that are refractory to all other pain therapies, when **all** of the following criteria, clearly documented in the patient's record, are met:

- The implantation of the stimulator is used only as a late or last resort for patients with chronic pain (present for ≥ three months); **and**
- Other treatment modalities (pharmacological, surgical, physical or psychological therapies) have been tried and did not prove satisfactory or are judged unsuitable or contraindicated for the given patient; **and**
- All of the facilities, equipment, and professional and support personnel required for the proper diagnosis, treatment, training, and follow-up of the patient must be available; **and**
- Demonstration of pain relief with a temporarily implanted electrode precedes permanent implantation (revision or replacement of the pulse generator, electrodes or receiver does not require a trial).

Spinal cord stimulation does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** in all other situations including but not limited to treatment of critical limb ischemia to forestall amputation, treatment of refractory angina pectoris, heart failure and cancer-related pain.

Dorsal root ganglion neurostimulation **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** for all indications.

Effective for dates of service April 8, 2014 through September 28, 2016:

Spinal cord stimulation meets Blue Cross and Blue Shield Alabama's medical criteria for coverage for the treatment of **severe and chronic pain of the trunk or limbs** that are refractory to all other pain therapies, when **all** of the following criteria, clearly documented in the patient's record, are met:

- The implantation of the stimulator is used only as a late or last resort for patients with chronic pain (present for ≥ three months); **and**
- Other treatment modalities (pharmacological, surgical, physical or psychological therapies) have been tried and did not prove satisfactory or are judged unsuitable or contraindicated for the given patient; **and**
- All of the facilities, equipment, and professional and support personnel required for the proper diagnosis, treatment, training, and follow-up of the patient must be available; **and**
- Demonstration of pain relief with a temporarily implanted electrode precedes permanent implantation (revision or replacement of the pulse generator, electrodes or receiver does not require a trial).

Spinal cord stimulation does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** in all other situations including but not

limited to treatment of critical limb ischemia to forestall amputation, treatment of refractory angina pectoris, heart failure and cancer-related pain.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

This policy is updated regularly with searches of the MEDLINE database. The most recent literature search was through February 05, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Refractory Chronic Trunk or Limb Pain

Standard Spinal Cord Stimulation

Systematic Reviews

Existing randomized controlled trials (RCTs) of standard spinal cord stimulation (SCS) for chronic trunk or limb pain are summarized in the next section. Five systematic reviews have assessed the RCTs included in the next section and overlap substantially. The North et al (2005) and Kumar et al (2007) RCTs are included in 3 systematic reviews; Kemler et al (2000) is included in 3 reviews, and Kapural et al (2015) included in one of the systematic reviews.

Two systematic reviews have focused on SCS specifically for complex regional pain syndrome (CRPS). Visnjevac et al (2017) reported on results of a systematic review of RCTs and observational studies of SCS for CRPS. The Kemler (2000) trial was the only RCT included, and it is discussed in the following section. The Cochrane overview of systematic reviews by O'Connell et al (2013) also focused on reviews of CRPS. The overview included reports from the Kemler RCT. Reviewers concluded that there was very low quality evidence using GRADE criteria that SCS using physical therapy was effective at reducing pain or improving quality of life in CRPS compared with physical therapy alone for up to 2 years.

In 2016, Grider et al reported results of a systematic review of RCTs of SCS for chronic spinal pain. Six RCTs meeting selection criteria were identified; 3 RCTs reported on the efficacy of standard SCS, while 3 assessed adaptive stimulation, high-frequency SCS (discussed below), and burst stimulation. Of the 3 RCTs assessing standard SCS, 2 were considered high quality and 1 moderate quality based on Cochrane criteria and Interventional Pain Management Techniques–Quality Appraisal of Reliability and Risk of Bias Assessment. Kapural et al (2015) will be discussed below in the section on high-frequency SCS. In the North and Kumar RCTs, SCS was associated with higher rates of pain relief than the comparator groups.

Two systematic reviews have focused on SCS for failed back surgery syndrome (FBSS), defined as persistent pain after spinal surgery and the initial pain may have been secondary to various causes. Kapural et al (2017) reported on a systematic review of prospective studies of SCS for FBSS. The North and Kumar trials were the only RCTs included and are discussed in the following section. In 2009, a systematic review of randomized controlled trials (RCTs) and observational studies of spinal cord stimulation (SCS) in failed back surgery syndrome (FBSS; defined as persistent pain after spinal surgery; the initial pain may have been secondary to various causes) was undertaken by Frey et al. The 2 RCTs, by North and Kumar were included. Using U.S Preventive Services Task Force quality ratings, the authors found Level II-1 evidence (from well-designed controlled trials without randomization) or II-2 evidence (from well-designed cohort or case-control analytic studies, preferably from more than one center or research group) for clinical use of the treatment on a long term-basis.

Also in 2009, Simpson et al reported on a health technology assessment, funded by the National Institute for Health and Care Excellence (NICE), to obtain clinical and cost-effectiveness data for SCS in adults with chronic neuropathic or ischemic pain with inadequate response to other medical or surgical treatments. NICE used the assessment as the basis for its guidance on SCS for chronic pain. Trials for FBSS and complex regional pain syndrome (CRPS) type I (reported by North et al [2005], Kumar et al [2007], and Kemler et al [2004, 2000]), suggested that SCS was more effective than conventional medical management or reoperation in reducing pain.

Randomized Controlled Trials

Five RCTs (total N=310 patients; range, 36-100 patients) have evaluated SCS (see Table 1). Patient populations had FBSS, diabetic neuropathy, and CRPS. The comparators were primarily conventional medical management, although 1 RCT compared to reoperation for FBSS, and another compared SCS to physical therapy. All RCTs reported results at 6 months. The most common primary outcome reported was a responder outcome of 50% reduction in pain; Kemler et al (2000) reported absolute change in visual analog scale (VAS) pain score. Consistent with

clinical practice, RCTs included a trial period of SCS, usually a few days to a week. Patients not reporting improvement in pain during the trial period did not continue receiving SCS during the remainder of follow-up. In most RCTs, these patients were included in the intention-to-treat analyses either as failures to respond or using imputation techniques. All RCTs with the responder primary outcomes reported clinically and statistically significant differences in the primary outcomes at 6 months, favoring SCS (SCS range, 39%-63% vs comparator range, 5%-12%). Outcomes measuring reduction in analgesic use were consistently numerically larger for SCS but not statistically significant in all studies. Four of the five studies did not report differences in functional, quality of life, or utility outcomes. Device-related complications ranged from 17% to 32%, with the most common being infection and discomfort or pain due to positioning or migration of electrodes or leads. However, 2 studies reported dural puncture headaches and Slangen et al (2014) reported a dural puncture headache ending in death. Two studies reported longer term results for both treatment groups. In each, results continued to favor SCS at 2 years but in the 1 study with 5 years of follow-up, results were not statistically significant at 5 years.

Section Summary: Standard Spinal Cord Stimulation for Refractory Chronic Trunk or Limb Pain
The evidence on the efficacy of standard SCS for treatment of chronic limb or trunk pain consists of 5 RCTs (range, 36-100 patients) with refractory pain due to FBSS, CRPS, or diabetic neuropathy. These trials were heterogeneous in terms of patient populations and participants were un-blinded (no trials used sham surgeries or devices) but they consistently reported improvements in pain with clinically and statistically significant effect sizes and reductions in medication use for at least 6 months. Even with a sham surgery or device, blinded outcomes assessment may not be feasible for SCS, because active SCS stimulation is associated with paresthesias. Given the large treatment effects with consistent findings across studies, this evidence suggests that SCS is a reasonable treatment option.

Table 2: Characteristics and Result of RCTs Using Standard SCS

Study	Population	Interventions	N at Baseline and Follow-Up	Results				Complications
				Outcome Measures	Int	Ctrl	p	
North et al (2005)	FBSS	• SCS + CMM • Reoperation + CMM	N=60 N at 6 mo=49	6 months (SCS vs reoperation)				17% device-related complications (infections, hardware technical problems)
				• Success (50% pain relief and patient satisfaction)	39%	12%	0.04	
				• Stable or decreased opioids	87%	58%	0.025	
				• No difference in ADLs impairment due to pain				
Kumar et al (2007, 2008)	FBSS with neuropathic pain	• SCS + CMM • CMM	N=100 N at 6 mo=93	6 months (SCS vs CMM)				32% device-related complications (electrode migration, infection, loss of paresthesia)
				• 50% reduction in VAS leg pain	48%	9%	<0.001	
				• SF-36, favoring SCS all domains except RP			≤0.02	
				• ODI score	45	56	<0.001	
				• Opioid use	56%	70%	0.21	
				• NSAIDs use	34%	50%	0.14	
			N at 24 mo=87	24 months (SCS vs CMM)				
				• 50% reduction in leg pain on VAS	37%	2%	0.003	
Kemler et al (2000, 2004, 2008)	CRPS	• SCS + PT • PT	N=54 N at 6 mo=54	6 months (SCS vs PT)				• 25% device-related complications (dural puncture, infection, unsatisfactory placement of electrode, defective lead) • 42% reoperation rate by 5 y

Study	Population	Interventions	N at Baseline and Follow-Up	Results				Complications
				• Reduction in VAS pain score	2.4	0.2	<0.001	
				• Much improved GPE	39%	6%	0.01	
				• No difference in functional outcomes or HRQOL				
				2 years (SCS vs PT)				
				• Reduction in VAS pain score	2.1	0.0	<0.001	
				• Much improved GPE	43%	6%	0.001	
			N at 5 y=44	5 years (SCS vs PT)				
				• Reduction in VAS pain score	1.7	1.0	0.25	
Slangen et al (2014)	Diabetic neuropathy of LEs	• SCS • CMM	N=36 N at 6 mo=36	6 months (SCS vs CMM)				2 SAEs (1 infection, 1 post-dural puncture headache ending in death)
				• Success (50% reduction in pain for 4 d or at least much improved on patient-reported global impression of change)	59%	7%	<0.01	
				• Reduction in pain medication	32%	0%		
				• No differences in health utility or HRQOL				
			N at 24 mo=17 (SCS only)	2 years (SCS only)				
				• Success	65 %			
				• No improvement in health utility vs baseline				
				• ≈5-point improvement in SF-36 PCS score vs baseline				
De Vos et al (2014); Duarte et al (2016)	Diabetic neuropathy of LEs	• SCS • CMM	N=60 N at 6 mo=54	6 months (SCS vs CMM)				18% device-related complications (infection, pain due to pulse generator or migration of lead, unsatisfactory placement of electrode)

Study	Population	Interventions	N at Baseline and Follow-Up	Results				Complications
				• 50% reduction in pain	62.5 %	5%	<0.001	
				• Reduction in analgesic intake (MQS score)	2.9	-0.09	NR	
				• Change in health utility	0.39	0.00	<0.05	

ADL: activities of daily living; CMM: conventional medical management; CRPS: complex regional pain syndrome; ctrl: control; FBSS: failed back surgery syndrome; GPE: global perceived effect; HRQOL: health-related quality of life; Int: intervention; LE: lower extremities; MQS: Medication Quantification Scale III; NR: not reported; NSAID: non-steroidal anti-inflammatory drug; ODI: Oswestry Disability Index; PCS: Physical Component Summary; PT: physical therapy; RP: role-physical; SAE: serious adverse events; SCS: spinal cord stimulation; SF-36: 36-Item Short-Form Health Survey; VAS: visual analog scale.

High-Frequency Spinal Cord Stimulation

In 2015, an SCS device, using a higher frequency of electrical stimulation (10 kHz) than predicate devices (which use frequencies on the order of 100-1000 Hz) was approved by the FDA. Studies that offer direct comparisons between standard SCS and high-frequency SCS (HFSCS) were sought to evaluate the incremental benefit of HFSCS.

Systematic Reviews

In 2016, Bicket et al published a systematic review of controlled trials on HFSCS. Reviewers searched for RCTs and controlled nonrandomized studies in adults with pain for at least 3 months who were treated with HFSCS (i.e., ≥1000 Hz) and prospectively assessed pain outcomes. Eight studies met these inclusion criteria; 2 RCTs (discussed in detail below) and 6 controlled nonrandomized studies. Both RCTs and 5 of 6 controlled studies addressed low back pain; the remaining controlled study addressed migraine. Reviewers used the Cochrane risk of bias tool to rate bias in the RCTs. One trial (Perruchoud et al, 2013) was not rated as having a high-risk of bias in any domain and the other (Kapural et al, 2015) was rated as having a high risk of bias in the domain of performance and detection bias because it was un-blinded. Studies were reviewed qualitatively (i.e., study findings were not pooled).

Randomized Controlled Trials

Three RCTs identified addressed HFSCS (see Table 2): Perruchoud et al (2013) compared high-frequency stimulation (5000 Hz ;) with sham control in a crossover design (N=40), while Kapural et al (2015) (N=198) and De Andres et al (2017) (N=60) both compared HFSCS (10,000 Hz) with standard SCS. The 3 trials had distinct patient populations and designs such that the results could not be synthesized.

The Perruchoud population (2013) was distinct from other trials of SCS or HFSCS in that it included patients who had chronic, treatment-refractory back pain previously treated with standard SCS (i.e., patients were not treatment-naive to SCS). Perruchoud et al used a 2×2 crossover design with a run-in and washout period consisting of standard SCS. In the trial treatment periods, patients were treated with HFSCS or sham stimulation. Outcomes were reported after 2 weeks of treatment. Forty-two percent were responders in the high-frequency group versus 30% in the sham group. The mean benefit averaged over the 2 crossover sequences was 11% favoring HFSCS (p=0.30). There were no differences between HFSCS and sham for VAS or health utility scores. However, there was a significant period effect: patients were more likely to respond in the first treatment period of the sequence regardless of sequence assignment. It is difficult to compare the Perruchoud findings to other RCTs due to the enrolled population (only people who had chronic pain despite previous use of standard SCS), the short treatment period (2 weeks), the period effect (patients tended to report greater pain reduction in first period regardless of assigned sequence), and the use of standard SCS during the 2 weeks preceding each treatment period, which could lead to carryover effects.

Kapural et al (2015, 2016) included patients with chronic leg and back pain who had received conventional medical management but not SCS. Kapural et al (2015) included an active but un-blinded comparator (standard SCS). Kapural (2015) included a trial SCS period up to 2 weeks post-randomization after which only responders continued with stimulation. Outcomes were reported after 3, 12, and 24 months of treatment. Response in the standard SCS group was

similar to previous trials of SCS, between 45% and 50% for back pain and 50% to 55% for leg pain at 3, 12, and 24 months. Response was clinically and statistically significantly higher with HFSCS than with SCS for both back (range, 75% to 85%) and leg pain (range, 70% to 85%) at all time points. A limitation of Kapural trial was that non-responders during the stimulation trial period were excluded from statistical analysis. Instead, assuming patients who were not implanted were non-responders corresponds to response rates at 3 months of about 75% in HFSCS versus 37% in SCS for back pain and 74% versus 46% for leg pain (calculated, data not shown).

De Andres et al (2017) included adults from a single center in Spain with FBSS refractory to standard treatment for at least 6 months with a pain intensity score of at least 5 out of 10 of a numeric rating scale (NRS). The comparator was SCS, and the trial was described as blinded, but the method of blinding participants was not given. Patients were told that the 2 treatments were "equally effective." Outcome assessors were reportedly blinded although many of the assessments used were patient-reported. Outcomes were reported at 3, 6, and 12 months. The primary outcome was "a reduction of at least 50% in pain intensity in the NRS score in the 12-month evaluation"; however, analysis of this outcome was not reported in the tables or text. The sample size calculations were unclear. Seventy-eight participants were assessed for eligibility, and 60 were randomized. It is unclear how many of the 18 not randomized were ineligible due to lack of response during the trial SCS period. Of the 60 randomized, 55 were included in the analysis. Although pain ratings improved in both groups, there were no statistically significant differences in change in NRS or Oswestry Disability Index scores from baseline at any of the follow-up visits between groups. Lead migration during follow-up was similar in both groups. No patients developed an infection at the implant site. Because of poor reporting, this trial is difficult to evaluate.

Table 3: Characteristics and Result of RCTs of Using HFSCS

Study	Population	Interventions	N at Baseline and Follow-Up	Results				Complications
				Outcome Measure	**Int**	**Ctrl**	**p**	
Perruchoud et al (2013)	Chronic low back pain radiating in 1 or both legs; previously treated with SCS	• HFSCS • Sham • 2×2 crossover design with conventional SCS before both arms	N=40 n=33	2 wk (HFSCS vs sham)				One patient had malaise attributed to a vasovagal attack
				• Responder (at least minimal improvement on patient-reported global impression of change)	42%	30%	0.30	
				• VAS score	4.35	4.26	0.82	
				• Health utility	0.48	0.46	0.78	
Kapural et al (2015, 2016)	Chronic back and leg pain	• HFSCS • SCS	N=198 n at 3 mo.=171 n at 24 mo.=156	3 mo. (HFSCS vs SCS)				• Stimulation discomfort, 0% vs 47% • No stimulated-rated SAEs or neurologic deficits
				• Responder (≥50% back pain reduction with no stimulation-related neurologic deficit): o Back pain	85%	44%	<0.001	
				o Leg pain	83%	55%	<0.001	
			n at 12 mo.=171	12 mo. (HFSCS vs SCS)				
				• Responders o Back pain	80%	50%	NR	
				o Leg pain	80%	56%	NR	
				• Decreased opioid use	36%	26%	0.41	
				• Improvement in ODI score	16.5	13.0	NR	
				24 mo. (HFSCS vs SCS)				
				• Responders o Back pain	77%	49%	<0.001	
				o Leg pain	73%	49%	<0.001	
De Andes et al (2017)	FBSS	• HFSCS • SCS	N=60 n=55	12 mo. (HFSCS vs SCS)				

analyzed				
	Responder (≥50% in pain intensity in NRS score at 12 mo.)[a]	NR	NR	
	Improvement in NRS score	6.1	5.9	0.56
	Improvement in ODI score	23.0	22.1	0.96

Ctrl: control; FBSS: failed back surgery syndrome; HFSCS: high-frequency spinal cord stimulation; Int: intervention; NR: not reported; NRS: numeric rating scale; ODI: Oswestry Disability Index; SAE: serious adverse events; SCS: spinal cord stimulation; VAS: visual analog scale.
a Despite the responder criteria being stated to be the primary outcome, the results for not reported in the report.

Case Series
Because RCT data are available for HFSCS, case series are discussed if they add information not available from the RCTs (e.g., longer follow-up, data on an important subgroup).
Al-Kaisy et al (2017) reported 36-month results for 20 patients with chronic low back pain without previous spinal surgery who were treated with 10-kHz HFSCS. Seventeen patients completed the 36-month follow-up; 1 patient died (unrelated to study treatment), 1 patient was explanted due to lack of efficacy, and 1 patient had new leg pain. Among patients analyzed, the mean VAS score for pain intensity decreased from 79 to 10 mm ($p<0.001$) and the mean Oswestry Disability Index score decreased from 53 to 20 ($p<0.001$). At baseline, 90% of the patients were using opioids compared with 12% at 36 months.

Section Summary: High-Frequency Spinal Cord Stimulation for Chronic Trunk or Limb Pain
The evidence for HFSCS compared to standard SCS consists of 1 RCT that randomized 198 patients not previously treated with SCS and reported a clinically and statistically significant benefit associated with HFSCS. The crossover RCT enrolling patients with pain despite previous treatment with SCS reported no difference between HFSCS and sham stimulation. However, interpretation on this trial is limited due to the significant period effect.

SCS with Burst Stimulation
In 2016, a supplement to an SCS device (in the form of a clinician programmer app), which allows for the provision of burst stimulation, was approved by FDA. Studies that offer direct comparisons between standard SCS and burst SCS were sought to permit evaluation of the incremental benefit of burst SCS.

Systematic Reviews
In 2016, Hou et al published a systematic review of burst SCS for treatment of chronic back and limb pain. Reviewers identified 5 studies of burst SCS in patients with intractable chronic pain of more than 3 months in duration who had failed conservative treatment. Three studies, with sample sizes of 12, 15, and 20, respectively, used randomized crossover designs to compare burst stimulation with tonic stimulation; 2 studies also included a placebo stimulation intervention. In addition, there were 2 case series with sample sizes of 22 and 48 patients, respectively. Data were collected after 1 to 2 weeks of treatment. Study findings were not pooled. Using American Association of Neurology (AAN) criteria, reviewers originally rated 4 studies as class III and 1 study as class IV. However, given the small sample sizes and short-term duration of the 4 studies, they were downgraded to class IV. Overall, the level of confidence in the evidence on burst SCS for treating chronic pain without paresthesia was rated as “very low”.

Randomized Controlled Trials
Five crossover RCTs with a total of 180 patients (range, 12-100 patients) were identified, 4 of which were conducted in Europe and the other in the United States (see Table 4). The trials by De Ridder et al (2010, 2013) enrolled patients with neuropathic pain, the trial by Schu et al (2014)39 enrolled patients with FBSS, Kriek et al (2017)40 enrolled patients with CRPS, and Deer et al (2018)41 enrolled patients with chronic intractable pain of the trunk and/or limbs. All trials compared burst stimulation with SCS. Schu (2014), De Ridder (2013), and Kriek (2017) also compared burst with a sham stimulation group. Schu (2014) included patients receiving

standard SCS while De Ridder (2010, 2013) and Deer (2018) included patients not previously treated with SCS. It was not clear in Kriek (2017) whether patients had previously received SCS. Results were reported for 1 week of stimulation in Schu (2014) and De Ridder (2013), and after two, 1-hour sessions of SCS or burst in De Ridder (2010), after 2 weeks of stimulation in Kriek (2017), and after 12 weeks of stimulation in Deer (2018). All trials reported reductions in absolute pain scores (NRS or VAS). Schu (2014) and De Ridder (2013) did not account for their crossover designs in data analyses, so analyses and p values are incorrect and not reported in Table 3. De Ridder (2010) did not provide between-group comparisons. Kriek reported only per-protocol analyses. Four trials reported numerically larger reductions in pain scores with burst than with SCS; Kriek (2017) did not report less pain for SCS at any frequency compared with burst. In Kriek (2017), 48% of patients preferred the 40-Hz SCS compared with 21%, 14%, 14%, and 3% that preferred 500-Hz SCS, 1200-Hz SCS, and burst and sham, respectively. The interpretation of the four of the trials was limited by small sample sizes, short follow-up, and incorrect, inadequate, or missing statistical analyses.

The largest trial of burst stimulation is the Success Using Neuromodulation with BURST (SUNBURST) trial reported by Deer et al (2018).41 SUNBURST was a 12-week, multicenter, randomized, unblinded, crossover, noninferiority trial evaluating traditional SCS or burst stimulation in 100 patients with chronic pain of the trunk and/or limbs enrolled between January 2014 and May 2015. Patients were SCS-naive and completed a trial stimulation period. Forty-five patients were randomized to SCS then burst, and the remaining 55 were randomized to burst then SCS. At the end of the second crossover period, patients were allowed to choose the stimulation mode they preferred and were followed for 1 year. Patients' mean age was 59 years; 60% of patients were women; and 42% of patients had FBSS while 37% had radiculopathies. The primary outcome was the difference in mean VAS score, with a noninferiority margin of 7.5 mm. Analyses were intention-to-treat with missing values imputed using the hot deck method. Also, outcomes were imputed for patients who underwent invasive procedures for pain or had medication increases. The estimated difference in the overall VAS score between burst and SCS was -5.1 mm (95% upper confidence interval [CI], -1.14 mm), demonstrating noninferiority ($p<0.001$) and superiority ($p<0.017$). The proportion of patients with a decrease in VAS score of 30% or more was 60% (60/100) during burst stimulation and 51% (51/100) during SCS. The proportion of patients whose global impression was minimally improved, moderately improved, or very much improved was approximately 74% in both groups. There were no significant differences in Beck Depression Inventory scores ($p=0.230$). Patients were asked to rate their satisfaction levels for both periods: 78% were satisfied with both SCS and burst, 4% were dissatisfied with both SCS and burst, 7% were satisfied with SCS but not burst, and 10% were satisfied with burst but not SCS. However, more patients (70.8%) reported preferring burst stimulation over SCS stimulation after the 24-week crossover period. After 1 year of follow-up, 60 (68%) of the 88 patients completing follow-up reported preferring burst stimulation. The authors reported that the programming parameters were not standardized at the beginning of the study but a more standardized approach with lower amplitudes was implemented as the trial was ongoing. Trial limitations included the crossover design, which limits comparison of pain over longer periods of time, lack of blinding, and variable burst programming parameters.

Section Summary: SCS with Burst Stimulation for Chronic Trunk or Limb Pain
SCS with burst stimulation has been evaluated in 5 crossover RCTs. Four of the RCTs had fewer than 35 patients. Inferences drawn from these trials are limited by small sample sizes, short follow-up, and flawed statistical analyses. The largest RCT (SUNBURST) was a 12-week, multicenter, randomized, unblinded, crossover, noninferiority trial assessing traditional SCS or burst stimulation in 100 patients with chronic pain of the trunk and/or limbs. The burst was noninferior to SCS for overall VAS score (at 12 weeks). The proportion of patients whose global impression was improved (minimally, moderately, or very much improved) was approximately 74% in both groups. Seventy-eight percent of patients reported being satisfied with both SCS and burst at the end of the 24-week crossover portion of the trial, while 7% were satisfied with SCS but not burst and 10% were satisfied with burst but not SCS. However, more patients (70.8%) reported preferring burst stimulation over SCS stimulation after the 24-week crossover.

Table 4: RCTs of Burst Spinal Cord Stimulation

Study	Population	Interventions	N at Baseline and FU	Results				Complications
3×3 crossover design without washout				**Outcome Measure**	**Burst**	**SCS**	**Sham**	
Schu et al (2014)	FBSS	• Burst stimulation • SCS • No stimulation (sham-control)	N=20 n=20	1 wk (burst vs SCS vs sham)[a]				No SAEs reported
				• Mean NRS pain intensity scores, favoring burst	4.7	7.1	8.3	
				• Mean SF-MPQ pain quality scores, favoring burst	19.5	28.6	33.5	
				• Mean ODI scores, favoring burst	19.8	24.6	29.5	
De Ridder et al (2013)	Neuropathic limb pain	• Burst stimulation • SCS • No stimulation (sham-control)	N=15 n=15	1 wk (burst vs SCS vs sham)[a]				Not reported
				• Mean improvement in VAS scores o Back pain	3.8	2.2	1.4	
				o Limb pain	3.9	3.9	0.9	
2×2 crossover								
De Ridder et al (2010)	Neuropathic pain	• Burst stimulation • SCS	N=12 n=unclear	Two 1-h sessions (burst vs SCS)[b]				Not reported
				• Mean improvement in VAS scores o Axial pain	5.3	1.8		
				o Limb pain	7.3	4.4		
				• Improvement in SF-MPQ sensory scores	16.7	8.6		
				• Improvement in SF-MPQ affective scores	6.7	4.3		
Deer et al (2018)	Chronic intractable pain of the trunk and/or	• Burst stimulation • SCS	N=100	12 wk (burst vs SCS)				2 study-related SAEs (persistent pain and/or numbness and 1 unsuccessful lead

	limbs							placement); 21 SAEs in total; 158 total adverse events in 67 patients
				Mean VAS scores at end of period, favoring burst	Diff = -5.1 mm (noninferiority p<0.001			
				Responder (≥30% improvement in VAS score)	60%	51%		
5×5 crossover								
Kriek et al (2017)	CRPS	• Burst stimulation • SCS 40 Hz • SCS 500 Hz • SCS 1200 Hz • No stimulation (sham-control)	N=33 n=29	2 wk (burst vs SCS at 40, 500, and 1200 Hz vs sham)				No SAEs reported; 3 electrodes became dislodged; 2 patients reported itching
				• Mean VAS scores at end of period	48	40[c]	64	
				• Mean global perceived effect (7-point scale where 7 [very satisfied] to 1 [not at all satisfied])	4.7	5.3[c]	3.5	

CRPS: complex regional pain syndrome; Diff: difference; FBSS: failed back surgery syndrome; FU: follow-up; NRS: numeric rating scale; ODI: Oswestry Disability Index; SAE: serious adverse events; SCS: spinal cord stimulation; SF-MPQ: Short-Form McGill Pain Questionnaire; VAS: visual analog scale.

a Analyses do not appear to take into account properly the crossover design; therefore, p values are not reported here.

b Statistical treatment comparisons not provided.

c Results from SCS 40 Hz reported here. Three different levels of SCS were given. Similar results were reported for the other 2 SCS levels and are not shown in this table..

Dorsal Root Ganglion Neurostimulators for Chronic Trunk or Limb Pain
Studies that offer direct comparisons between standard SCS and dorsal root ganglion (DRG) neurostimulators were sought to allow an evaluation of the incremental benefit of SCS.

DRG Implanted Device
Systematic Reviews
Chang Chien et al (2017) published a systematic review on intraspinal stimulation of nondorsal column targets, including neurostimulation of the DRG for chronic pain. Reviewers included reports published through March 2015. They identified 6 studies of DRG stimulation: 1 conference presentation of the preliminary RCT data from the ACCURATE trial (discussed below), 4 publications describing 3 prospective observational studies, and 1 retrospective chart review. In the 3 prospective observational studies (N=32, 10, and 8), follow-up ranged from 7 days to 12 months. The retrospective study reported on 25 patients with a follow-up to 32 weeks.

Randomized Controlled Trial
One RCT, the ACCURATE study (NCT01923285), compared DRG neurostimulators and standard SCS. The trial, published by Deer et al in 2017, was a multicenter un-blinded non-inferiority trial. Eligibility criteria included chronic (≥6 months) intractable (failed ≥2 drugs from different classes) neuropathic pain of the lower limbs associated with a diagnosis of CRPS or causalgia and no previous neurostimulation. Patients were randomized to DRG stimulation with the Axium device or to standard SCS. They first underwent a temporary trial of stimulation lasting 3 to 30 days, depending on the protocol at each site. Patients who had 50% or greater reduction in lower limb pain after the temporary trial were eligible for permanent stimulation. Those who failed temporary stimulation exited the trial, but were included in the analysis as treatment failures. Trial characteristics are shown in Table 5.

A total of 152 patients were randomized, and 115 (n=61 DRG, n=54 SCS) had a successful temporary trial and continued to permanent implantation. The primary outcome was a composite measure of treatment success. Success was defined as: (1) 50% or greater reduction in VAS score and (2) no stimulation-related neurologic deficits. The noninferiority margin was set at 10%. Results are shown in Table 6. No patients experienced neurologic deficits in either group. Regarding paresthesias, at 3 months and 12 months, SCS patients were significantly more likely to report paresthesias in nonpainful areas than DRG patients. At 3 months, 84.7% of DRG patients and 65% of SCS patients reported paresthesias only in their painful areas; at 12 months, these percentages were 94.5% and 61.2%, respectively. Gaps in study relevance, design, and conduct are shown in Tables 7 and 8.

Table 5. RCT Characteristics of DRG Implanted Devices

Study	Countries	Sites	Dates	Participants	Interventions: DRG	Interventions: SCS
Deer et al (2017): ACCURATE (NCT01923285)	U.S.	22	2013-2016	• CRPS or causal lower extremities • Chronic pain (≥6 mo.) • Stimulation-naïve • Failed ≥2 pharmacologic treatments	AXIUM Neurostimulator System (n=76)	RestoreUltra and RestoreSensor (n=76)

CRPS: complex regional pain syndrome; DRG: dorsal root ganglion; SCS: spinal cord stimulation.

Table 6. RCT Results of DRG Implanted Devices

Study	≥50% Reduction in VAS Scores for Pain	Physical Functioning	Emotional Functioning	Quality of Life		Safety
		Mean BPI Interference	**POMS Total Score**	**SF-36 PCS**	**SF-36 MCS**	**SAEs**
Deer et al (2017)						
At 3 months						
n	139	113	NR	113	113	NR
DRG	81%	4.2	NR	11.8	8.3	
SCS	56%	3.0	NR	9.4	4.8	
TE (95% CI) (p)	NR (noninferiority p<0.001; superiority p<0.001)	1.1 (0.2 to 2.1) (<0.05 favoring DRG)	NR (0.04 favoring DRG)	2.5 (-0.7 to 5.7)	3.5 (-0.5 to 7.5)	
At 12 months						
n	132	105	NR	105	105	152
DRG	74%	3.9	≈18	11.5	6.2	11%
SCS	53%	2.6	≈8	8.0	3.6	15%
TE (95% CI) (p)	NR (noninferiority p<0.001; superiority p<0.001)	1.3 (0.2 to 2.3) (<0.05 favoring DRG)	NR (<0.001)	3.5 (-0.1 to 7.1) (0.04 favoring DRG)	2.6 (-1.9 to 7.1)	NR (0.62)

BPI: Brief Pain Inventory; CI: confidence interval; DRG: dorsal root ganglion; MCS: Mental Component Summary; NR: not reported; NRS: numeric rating scale; POMS: Profile of Mood States; PCS: Physical Component Summary; RCT: randomized controlled trial; SAE: serious adverse event; SCS: spinal cord stimulation; SF-36: 36-Item Short-Form Health Survey; TE: treatment effect; VAS: visual analog scale.

Table 7. Relevance Gaps for RCTs of DRG Implanted Devices

Study	Population	Intervention	Comparator	Outcomes	Follow-Up
Deer et al (2017)	None noted	None noted	None noted	None noted	None noted
Key	1. Intended use population unclear 2. Clinical context for treatment is unclear 3. Study population unclear 4. Study population not representative of intended use 5. Study population is subpopulation of intended use	1. Not clearly defined 2. Version used unclear 3. Delivery not similar intensity as comparator	1. Not clearly defined 2. Not standard or optimal 3. Delivery not similar intensity as intervention 4. Not delivered effectively	1. Key health outcomes not addressed 2. Physiologic measures, not validated surrogates 3. Not CONSORT reporting of harms 4. Not established and validated measurements 5. Clinically significant difference not prespecified 6. Clinically significant difference not supported	1. Not sufficient duration for benefits 2. Not sufficient duration for harms

DRG: dorsal root ganglion; RCT: randomized controlled trial.

Table 8. Study Design and Conduct Gaps for RCTs of DRG Implanted Devices

Study	Allocation	Blinding	Selective Reporting	Follow-Up	Power	Statistical
Deer et al (2017)	None noted	1, 2. Patients and study staff not blinded. Outcomes mostly patient reported which could lead to bias. However, an active control (SCS) was used.	None noted	None noted	None noted	4. Treatment effects not reported for some outcomes but p values reported
Key	1. Participants not randomly allocated 2. Allocation not concealed 3. Allocation concealment unclear 4. Inadequate control for selection bias	1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician	1. Not registered 2. Evidence of selective reporting 3. Evidence of selective publication	1. High loss to follow-up or missing data 2. Inadequate handling of missing data 3. High number of crossovers 4. Inadequate handling of crossovers 5. Inappropriate exclusions 6. Not intent to treat analysis (per protocol for noninferiority trials)	1. Power calculations not reported 2. Power not calculated for primary outcome 3. Power not based on clinically important difference	1. Test is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event 2. Test is not appropriate for multiple observations per patient 3. Confidence intervals and/or p values not reported 4. Comparative treatment effects not calculated

DRG: dorsal root ganglion; RCT: randomized controlled trial; SCS: spinal cord stimulation.

Case Series
Two case series with more than 10 participants evaluating wireless injectable neurostimulators in patients with pain have been published. Two used the Axium device (Liem et al [2015], n=51; Schu et al [2015], n=29) and 1 used the Freedom SCS device (Weiner et al [2016], n=11). Liem et al published the series with the longest follow-up. Fifty-one patients with chronic pain of the trunk, lower back, or lower limbs who had failed conventional treatment underwent trial stimulation, and 32 underwent permanent implantation. From baseline to the 12-month follow-up, the mean VAS score decreased from 77.6 mm (n=32) to 33.6 mm (n=25; p<0.001). Sixty percent of patients achieved a 50% or greater reduction in overall pain.

DRG Wireless Injectable Device
No controlled studies were identified. A case series, which included 11 patients, was published by Weiner et al in 2016. The study included patients with FBSS who had chronic intractable neuropathic pain of the trunk and/or lower limbs. Five patients participated in phase 1 of the study (device not anchored) and 6 participated in phase 2 (device anchored). During phase 1, the device migrated more than was recommended and thus it was anchored in the remaining patients. Baseline VAS was ≥5 in all patients. Seven of the eleven patients (63%) reported good to excellent overall pain relief (≥50% reduction in VAS), 2 patients reported fair overall intensity pain relief (25–50% reduction), and 2 patients reported poor or no overall pain relief (0–25%). No adverse events were reported.

Section Summary: DRG Neurostimulators for Chronic Trunk or Limb Pain
One un-blinded RCT and several case series have evaluated wireless neurostimulators in patients with chronic trunk and/or limb pain. The RCT (N=152) found that patients receiving wireless injectable stimulators had significantly higher rates of treatment success at 3 and 12 months than those receiving standard SCS devices. Both groups experienced paresthesias, but patients in the DRG group reported less postural variation in paresthesia and reduced extraneous stimulation in nonpainful areas. Patients in the DRG group also reported more improvement in interference with physical functioning and mood states. Rates of serious adverse events were similar. Several case series have also been published. The largest series, which had the longest follow-up, found that 60% of patients had 50% or greater reduction in overall pain at 12 months. While outcomes have been favorable, additional RCTs are needed to provide greater certainty in the treatment benefit.

Critical Limb Ischemia
Critical limb ischemia is described as pain at rest or the presence of ischemic limb lesions. Amputation may be required if patients are not suitable candidates for limb revascularization (typically due to insufficient distal runoff). SCS has been investigated in this subset of patients as a technique to relieve pain and decrease the incidence of amputation.

A systematic review from the Cochrane group on the use of SCS in peripheral vascular diseases was updated in 2013. The review included RCTs and non-RCTs evaluating the efficacy of SCS in adults with non-reconstruct able chronic critical leg ischemia. Six trials were identified; all were conducted in Europe and 5 were single-country studies. SCS was compared with other nonsurgical interventions. One study was not randomized and none was blinded. In a pooled analysis of data from all 6 studies, there was a significantly higher rate of limb survival in the

SCS group than in the control group at 12 months (pooled risk difference [RD], -0.11; 95% CI, -0.20 to -0.02). The 11% difference in the rate of limb salvage means that 9 patients would need to be treated to prevent 1 additional amputation (95% CI, 5 to 50 patients). However, when the nonrandomized study was excluded, the difference in the rate of amputation no longer differed significantly between groups (RD = -0.09; 95% CI, -0.19 to 0.01). The SCS patients required significantly fewer analgesics, and more patients reached Fontaine stage II (intermittent claudication) than in the control group. There was no difference in ulcer healing (but only 2 studies were included in this analysis). In the 6 trials, 31 (15%) of 210 patients had a change in stimulation requiring intervention, 8 (4%) experienced end of battery life, and 6 (3%) infections required device removal.

Previously, in 2009, Klomp et al published a meta-analysis that was limited to RCTs on SCS in patients with critical limb ischemia. The same 5 RCTs identified in the Cochrane review, described above, were included. The authors did not find a statistically significant difference in the rate of amputation in the treatment and control groups. There was a relative risk of amputation of 0.79 and a risk difference of -0.07 (p=0.15). The authors also conducted additional analyses of data from their 1999 RCT to identify factors associated with a better or worse prognosis. They found that patients with ischemic skin lesions had a higher risk of amputation compared to patients with other risk factors. There were no significant interactions between this or any other prognostic factor. The analyses did not identify any subgroup of patients who might benefit from SCS.

A 2015 systematic review of non-revascularization-based treatments, including SCS, for patients with critical limb ischemia also included 5 RCTs. In pooled analysis, the authors found that SCS was associated with reduced risk of amputation (odds ratio [OR] 0.53, 95% CI 0.36 to 0.79). However, the review authors concluded that there was "relatively low quality of the evidence mainly due to imprecision (i.e., small sample size and wide CIs) and the risk of bias."

Section Summary: Critical Limb Ischemia

Five relatively small RCTs comparing SCS with usual care have assessed patients with critical limb ischemia. In some pooled analyses of these RCTs, SCS did not result in a significantly lower rate of amputation, although 1 systematic review and meta-analysis reported a significant difference. This evidence is not sufficient to determine whether SCS would improve outcomes for patients with critical limb ischemia.

Refractory Angina Pectoris

Systematic Reviews

Several systematic reviews of the literature have evaluated SCS for treating angina pectoris. Most recently, in 2016, Pan et al identified 12 RCTs that evaluated SCS in patients with refractory angina pectoris. Most studies had small sample sizes (i.e., <50 patients) and together totaled 476 patients. Reviewers did not report the control interventions reported in the RCTs. Pooled analyses favored the SCS group in most cases (e.g., for exercise time after intervention, pain level [VAS score], angina frequency), but there was not a significant difference between intervention and control groups on physical limitation and angina stability.

In 2015, another systematic review was published by Tsigaridas et al. It included 9 RCTs evaluating SCS for refractory angina, 7 of which compared SCS to low or no stimulation and 2 of which compared SCS to alternative medical or surgical therapy for angina. Reviewers found that most RCTs were small and variable in quality based on assessment with the modified Jadad score. Reviewers reported: "two of the RCTs were of high quality (Jadad score 4); 2 were of low quality (Jadad score 1) and the remaining ones were of intermediate quality (Jadad score 2-3)." Most trials comparing SCS to low or no stimulation found improvements in outcomes with SCS; however, given limitations in the evidence base, reviewers concluded that larger multicenter RCTs would be needed to assess the efficacy of SCS for angina.

Randomized Controlled Trials

In 2012, Zipes et al published an industry-sponsored, single-blind, multicenter trial with sites in the United States and Canada. This trial was terminated early because interim analysis by the data and safety monitoring board found the treatment futility. A total of 118 patients with severe angina, despite maximal medical treatment, were enrolled in the trial. Of these, 71 (60%) patients underwent SCS implantation with the Intrel III neurostimulator (Medtronic). The remaining 47 patients did not meet eligibility criteria post-enrollment nor had other issues (e.g., withdrew consent). The investigators had originally been planning to randomize up to 310 patients, but enrollment was slow. Implantation was successful in 68 patients; this group was randomized to high-stimulation (n=32) or a low-stimulation control (n=36). The low-stimulation control was designed so that patients would feel paresthesia, but the effect of stimulation would be subtherapeutic. The primary outcome was a composite of major adverse cardiac events (MACE), which included death from any cause, acute myocardial infarction, or revascularization through 6 months. Fifty-eight (85%) of 68 patients contributed data to the 6-month analysis; analysis was by intention to treat. The proportion of patients experiencing MACE at 6 months did not differ significantly between groups (12.6% in the high-stimulation group vs 14.6% in the low-stimulation group; p=0.81). The trial sample size was small, and it might have been underpowered for clinically meaningful differences.

A small 2011 RCT from Italy by Lanza et al randomized 25 patients to 1 of 3 treatment groups: SCS with standard stimulation (n=10), SCS with low-level stimulation (75%-80% of the sensory threshold) (n=7), or very low intensity SCS (n=8). Thus, patients in groups 2 and 3 were unable to feel sensation during stimulation. After a protocol adjustment at 1 month, patients in the very low intensity group were re-randomized to one of the other groups after which there were 13 patients in the standard stimulation group and 12 patients in the low-level stimulation group. At the 3-month follow-up (2 months after re-randomization), there were statistically significant between-group differences in 1 of 12 outcome variables. There were a median of 22 angina episodes in the standard stimulation group and 10 in the low-level stimulation group (p=0.002). Nonsignificant variables included use of nitroglycerin, QOL (VAS), Canadian Cardiovascular Society angina class, exercise-induced angina, and scores on 5 subscales of the Seattle Angina Questionnaire.

Section Summary: Refractory Angina Pectoris

Numerous small RCTs have evaluated SCS as a treatment for refractory angina. While some studies have reported benefit, most have not. In 2 more recent RCTs, there was no significant

benefit for the primary outcomes. Overall, this evidence is mixed and insufficient to permit conclusions on whether health outcomes are improved.

Heart Failure

Findings of a small pilot crossover RCT evaluating SCS for heart failure were published in 2014 by Torre-Amione et al. Eligibility included symptomatic heart failure despite optimal medical therapy, left ventricular ejection fraction less than 30%, hospitalization or need for intravenous inotropic support in the past year, and ability to walk less than 450 meters on a six-minute walk test. All patients had an implanted heart device. Nine patients underwent SCS implantation and received three months of active treatment and three months of inactive treatment (off position), in random order. There was a one month washout period between treatments. The primary outcome was a composite of death, hospitalization for worsening heart failure, and symptomatic bradyarrhythmia or tachyarrhythmia requiring high-voltage therapy. Four patients experienced at least one of the events in the composite end point. The event occurred in 2 patients while the device was turned on and 2 while it was turned off. One patient died about 2 months after implantation while the device was turned off. The SCS devices did not interfere with the functioning of implantable cardioverter defibrillators.

In 2016, Zipes et al reported the results of the DEFEAT-HF trial, a prospective, multicenter, single-blind RCT trial comparing SCS with active stimulation to sham control in patients with New York Heart Association (NYHA) functional class III heart failure with left ventricular ejection fraction of 35% or less. A total of 66 patients were implanted with an SCS and randomized in a 3:2 manner to SCS ON (n=42) or SCS OFF (sham; n=24). For the study's primary endpoint, change in left ventricular end systolic volume index (LVESVi) from baseline to 6 months, there was no significant difference between groups (P=0.30). Other endpoints related to heart failure hospitalization and heart failure-related QOL scores and symptoms did not differ significantly between groups. After completion of the 6 month randomization period, all subjects received active SCS stimulation. From baseline to 12 months of follow-up, there were no significant treatment effects in the overall patient population in echocardiographic parameters (P=0.36). The study was originally powered based on a planned enrollment of 195 implanted patients, but enrollment was stopped early due to enrollment futility. The nonsignificant difference between groups may be the result of under-powering. However, the absence of any treatment effects or between-group differences is further suggestive of a lack of efficacy of SCS for heart failure.

Section Summary: Heart Failure

Two RCTs have evaluated SCS as a treatment for heart failure. One was a small pilot crossover trial (N=9 patients) that reported at least 1 adverse event in 2 patients with the device turned on and in 2 patients with the device turned off. The other RCT (N=66 patients) was sham controlled; it did not find significant differences between groups, but might have been underpowered.

Cancer-related Pain

In 2013, a Cochrane review by Lihua and colleagues was published on spinal cord stimulation for treatment of cancer-related pain in adults. The authors did not identify any RCTs evaluating the efficacy of SCS in patients with cancer-related pain. Four case series using a before-after

design with a total of 92 patients were identified. The Cochrane review was updated in 2015 (Peng et al), with no new studies meeting inclusion criteria identified. Peng et al concluded, "Current evidence is insufficient to establish the role of SCS in treating refractory cancer-related pain."

Section Summary: Cancer-Related Pain
A Cochrane review did not identify any RCTs evaluating SCS for treatment of cancer-related pain.

Potential Adverse Effects
Whereas RCTs are useful for evaluating efficacy, observational studies can provide data on the likelihood of potential complications. In 2010, Mekhail and colleagues published a retrospective review of 707 patients treated with SCS between 2000 and 2005. The patients' diagnoses included CRPS (n=345, 49%), failed back surgery syndrome (n=235, 33%), peripheral vascular disease (n=20, 3%), visceral pain in the chest, abdomen, or pelvis (n=37, 5%), and peripheral neuropathy (n=70, 10%). There was a mean follow-up of three years (range three months to seven years). A total of 527 of the 707 (36%) eventually underwent permanent implantation of an SCS device. Hardware-related complications included lead migration in 119 of 527 (23%) cases, lead connection failure in 50 (9.5%) cases, and lead break in 33 (6%) cases. Revisions or replacements were done to correct the hardware problems. The authors noted that rates of hardware failure have decreased in recent years due to advances in SCS technology. Documented infection occurred in 32 of 527 (6%) patients with implants; there were 22 cases of deep infection, and 18 patients had documented abscesses. There was not a significant difference in the infection rate by diagnosis. All cases of infection were managed by device removal.

In 2012, Lanza et al reviewed observational studies on SCS in patients with refractory angina pectoris. The authors identified 16 studies with a total of 1,204 patients (although they noted that patients may have been included in more than one report). The most frequently reported complications were lead issues, i.e., electrode dislodgement or fracture requiring repositioning, or internal programmable generator (IPG) failure during substitution. Lead issues were reported by ten studies with a total of 450 patients. In these studies, 55 cases of lead or IPG failure were reported. No fatalities related to SCS treatment were reported.

Summary of Evidence
Treatment-Refractory Chronic Pain
For individuals who have treatment-refractory chronic pain of the trunk or limb who receive standard spinal cord stimulation (SCS), the evidence includes systematic reviews and randomized controlled trials (RCTs). Relevant outcomes are symptoms, functional outcomes, quality of life, medication use, and treatment-related morbidity. Available RCTs are mixed in terms of the underlying diagnoses in select patient populations. However, those including patients with underlying neuropathic pain processes have shown a significant benefit with SCS. Systematic reviews have supported the use of SCS to treat refractory trunk or limb pain, and patients who have failed all other treatment modalities have few options. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have treatment-refractory chronic pain of the trunk or limbs who receive high-frequency SCS, the evidence includes 3 RCTs. Relevant outcomes are symptoms, functional outcomes, quality of life, medication use, and treatment-related morbidity. One RCT comparing high-frequency to standard SCS in patients who had not previously been treated with SCS found a clinically and statistically significant benefit associated with high-frequency SCS. Another RCT in patients who had chronic pain despite previous treatment with standard SCS found no benefit for those receiving high-frequency stimulation compared with sham control; however, it is difficult to compare these findings to other trials of SCS due to the different patient populations, short treatment periods, and the crossover period effect. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have treatment-refractory chronic pain of the trunk or limbs who receive wireless injectable dorsal root ganglion neurostimulation, the evidence includes 1 RCT and case series. Relevant outcomes are symptoms, functional outcomes, quality of life, medication use, and treatment-related morbidity. One unblinded RCT found that patients receiving DRG neurostimulation had significantly higher rates of treatment success at 3 and 12 months than those receiving standard SCS devices. Both groups experienced paresthesias, but patients in the DRG group reported less postural variation in paresthesia and reduced extraneous stimulation in nonpainful areas. Patients in the DRG group also reported more reduction in interference with physical functioning and mood states. Rates of serious adverse events were similar. Given that DRG neurostimulation targets a different portion of the sensory pathway and anatomic location than standard SCS, replication is needed in a confirmatory RCT. The evidence is insufficient to determine the effects of the technology on health outcomes.

Critical Limb Ischemia

For individuals who have critical limb ischemia who receive SCS, the evidence includes RCTs. Relevant outcomes are overall survival, symptoms, functional outcomes, quality of life, morbid events, hospitalizations, and treatment-related morbidity. In some pooled analyses of these RCTs, SCS did not result in a significantly lower rate of amputation, although 1 systematic review and meta-analysis did report a significant difference. The evidence is insufficient to determine the effects of the technology on health outcomes.

Treatment-Refractory Angina Pectoris

For individuals who have treatment-refractory angina pectoris who receive SCS, the evidence includes RCTs. Relevant outcomes are overall survival, symptoms, functional outcomes, quality of life, morbid events, hospitalizations, and treatment-related morbidity. Numerous small RCTs have evaluated SCS as a treatment for refractory angina. While some have reported benefit, most have not. In 2 more recent RCTs, there was no significant benefit on the primary outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Heart Failure

For individuals who have heart failure who receive SCS, the evidence includes RCTs. Relevant outcomes are overall survival, symptoms, functional outcomes, quality of life, morbid events,

hospitalizations, and treatment-related morbidity. One small pilot crossover study (N=9) reported at least 1 adverse event in 2 patients with the device turned on and in 2 patients with the device turned off. The other RCT (N=66) was sham controlled; it did not find significant differences between groups, but may have been underpowered to do so. The evidence is insufficient to determine the effects of the technology on health outcomes.

Cancer-Related Pain

For individuals who have cancer-related pain who receive SCS, the evidence includes no RCTs. Relevant outcomes are symptoms, functional outcomes, quality of life, medication use, and treatment-related morbidity. No RCTs evaluating SCS in this population were identified. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

International Association for the Study of Pain

In 2013, the Neuropathic Pain Special Interest Group of the International Association for the Study of Pain published recommendations on management of neuropathic pain. The interest group issued two recommendations on SCS; both were considered weak due to the amount and consistency of the evidence. The recommendations supported the use of SCS for failed back surgery syndrome and for complex regional pain syndrome.

American Society of Interventional Pain Physicians

In 2013, the American Society of Interventional Pain Physicians updated their evidence-based guidelines for interventional techniques in the management of chronic spinal pain. The guidelines included the statement that there is fair evidence in support of SCS in managing patients with failed back surgery syndrome.

An evidence-based guideline (2007) from ASIPP found the evidence for SCS in failed back surgery syndrome and CRPS strong for short-term relief and moderate for long-term relief. Reported complications with SCS ranged from infection, hematoma, nerve damage, lack of appropriate paresthesia coverage, paralysis, nerve injury, and death.

National Institute for Health and Clinical Excellence

In October 2008, the National Institute for Health and Clinical Excellence (NICE) issued a guideline on spinal cord stimulation for chronic pain of neuropathic or ischemic origin. The guideline stated that SCS is recommended as a treatment option for adults with chronic pain of neuropathic origin who continue to experience chronic pain (measuring at least 50 mm on a 0–100 mm VAS) for at least 6 months despite appropriate conventional medical management, and who have had a successful trial of stimulation as part of an assessment by a specialist team.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Key Words:

Neurostimulator, implantable spinal cord stimulator, spinal neurostimulators, electrical nerve stimulators, implantable electrical nerve stimulators, spinal cord stimulator, dorsal column

stimulator, angina, critical limb ischemia, pain management, Senza™ System HF10, Axium Neurostimulator System, wireless dorsal root ganglion neurostimulator, Freedom Spinal Cord Stimulator, BurstDR™ stimulation, Nevro Senza™, Genesis, Eon devices, Precision Spinal Cord Stimulator

Approved by Governing Bodies:

A large number of neurostimulator devices, some of which are used for spinal cord stimulation, have been approved by the U.S. Food and Drug Administration (FDA) through the premarket approval (PMA) process. Examples of fully-implantable SCS devices approved through the PMA process include the Cordis programmable neurostimulator (Cordis Corp., Downers Grove, IL), was approved in 1981, the Itrel® (Medtronic, Inc, Minneapolis, MN), approved in 1984, the Genesis and Eon devices (St. Jude Medical) and in 2001 the Precision Spinal Cord Stimulator (Advanced Bionics, LLC., Switzerland), approved in 2004.

In May 2015, the FDA approved the Nevro Senza™ Spinal Cord Stimulator (Nevro Corp., Menlo Park, CA), a totally-implantable neurostimulator device for the following indications: "chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with the following: failed back surgery syndrome, intractable low back pain, and leg pain." This device uses a higher frequency of electrical stimulation (10 kHz) than standard devices.

In February 2016, the Axium Neurostimulator System (Spinal Modulation, Menlo Park, CA) was approved by FDA through the PMA process. This is an implanted device that stimulates the dorsal root ganglion. It is indicated as an aid in the management of moderate-to-severe intractable pain of the lower limbs in adults with complex regional pain syndrome types I and II.

In August 2016, the Freedom Spinal Cord Stimulator (Stimwave Technologies, Fort Lauderdale, FL), a wireless injectable stimulator, was cleared for marketing by FDA through the 510(k) process for treating chronic, intractable pain of the trunk and/or lower limbs. The Freedom device has implanted/injected microstimulators that contain electrode(s). The microstimulators with electrodes are powered through a wireless pack worn externally (external battery pack). The device can be placed to target the spinal cord (i.e., levels T7 to L5) or to target the dorsal root ganglion.

In October 2016, FDA approved BurstDR™ stimulation (St. Jude Medical, Plano, TX), a clinician programmer application that provides intermittent "burst" stimulation for patients with certain St. Jude SCS devices.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP contracts: Special benefit consideration may apply. Refer to member's benefit plan.

Current Coding:

CPT Codes:

63650	Percutaneous implantation of neurostimulator electrode array; epidural
63655	Laminectomy for implantation of neurostimulator electrode plate/paddle; epidural
63661	Removal of spinal neurostimulator electrode percutaneous array(s), including fluoroscopy, when performed
63662	Removal of spinal neurostimulator electrode plate/paddle(s) placed via laminotomy or laminectomy, including fluoroscopy, when performed
63663	Revision including replacement, when performed, of spinal neurostimulator electrode percutaneous array(s), including fluoroscopy, when performed
63664	Revision including replacement, when performed, of spinal neurostimulator electrode plate/paddle(s) placed via laminotomy or laminectomy, including fluoroscopy, when performed
63685	Insertion or replacement of spinal neurostimulator pulse generator or receiver, direct or inductive coupling
63688	Revision or removal of implanted spinal neurostimulator pulse generator or receiver
95970	Electronic analysis of implanted neurostimulator pulse generator system (e.g. rate, pulse amplitude, pulse duration, configuration of wave form, battery status, electrode selectability, output modulation, cycling, impedance and patient compliance measurements); simple or complex brain, spinal cord, or peripheral (i.e. cranial nerve, peripheral nerve, sacral nerve, neuromuscular) neurostimulator pulse generator/transmitter, without programming
95971	; simple spinal cord, or peripheral (i.e., peripheral nerve, sacral nerve, neuromuscular) neurostimulator pulse generator/transmitter, with intraoperative or subsequent programming
95972	; complex spinal cord, or peripheral (i.e., peripheral nerve, sacral nerve, neuromuscular) (except cranial nerve) neurostimulator pulse generator/transmitter, with intraoperative or subsequent programming

HCPC Codes:

L8679	Implantable neurostimulator pulse generator, any type
L8680	Implantable neurostimulator electrode, each
L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
L8686	Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension
L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension

L8688	Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension

Previous Coding:

CPT Codes:

95973	; complex spinal cord, or peripheral (i.e., peripheral nerve, sacral nerve, neuromuscular) (except cranial nerve) neurostimulator pulse generator/transmitter, with intraoperative or subsequent programming, each additional 30 minutes after first hour (list separately in addition to code for primary procedure) **(Deleted effective 01/01/2016)**

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Policy History:

Medical Policy Group, November 2008 **(4)**
Medical Policy Administration Committee, December 2008
Available for comment November 25, 2008-January 8, 2009

Medical Policy Group, September 2010, **(1):** No change in coverage statement, Key Points updated, policy title change
Medical Policy Administration Committee, October 2010
Available for comment October 21 through December 6, 2010
Medical Policy Group, December 2011 **(1):** 2012 Code Updates – verbiage change on 95970, 95971, 95972, and 95973
Medical Policy Group, January 2012 **(1):** Update to Key Points related to MPP update; no change in policy statement
Medical Policy Panel, January 2013
Medical Policy Group, April 2013 **(1):** 2013 Update to Key Points and References; minor change in policy statement wording (changed "chronic ischemic limb" to "critical ischemic limb")
Medical Policy Panel, January 2014
Medical Policy Group, January 2014 **(1):** Update to Policy, Key Points and References related to change in policy statement to noncoverage of angina pain; update to Current Codes with addition of HCPCS code L8679 effective 01/01/2014
Medical Policy Administration Committee, February 2014
Available for comment February 20 through April 7, 2014
Medical Policy Group, May 2014 **(5):** 2014 Coding Update: Deleted code L8680 effective July 1, 2014.
Medical Policy Group, June 2014 **(5):** Quarterly 2014 Coding Update: Code L8680 did not delete added back to policy under current codes.
Medical Policy Panel, January 2015
Medical Policy Group, January 2015 **(6):** 2015 Updates – Description, Key Points and References, no change to policy statement
Medical Policy Group, November 2015: 2016 Annual Coding Update. Created previous coding section and moved CPT code 95973 from current coding to previous coding. Revised CPT code 95972.
Medical Policy Group, January 2016 **(6):** Update to Key Words and Approved by Governing Bodies to add Senza System.
Medical Policy Panel, April 2016
Medical Policy Group, April 2016 **(6):** Updates to Description, Policy, Key Points, Key Words, Approved by Governing Bodies and References; policy statement updated to add high frequency spinal cord stimulation as investigational for the treatment of severe and chronic pain of the trunk or limbs.
Medical Policy Administration Group, April 2016
Available for comment April 19 through June 2, 2016
Medical Policy Group, May 2016 **(5):** Removed reference to high frequency spinal cord stimulation from the policy. Added information: The available RCT comparing standard and high frequency stimulation is suggestive of a benefit to high frequency stimulation. Updates due to comments during the comment period Policy removed off of draft since policy statement went back to original statement.
Medical Policy Panel, April 2017
Medical Policy Group, June 2017 **(6)**: Updates to Policy statement, added "Wireless injectable dorsal root ganglion neurostimulation does not meet Blue Cross and Blue Shield of Alabama's

medical criteria for coverage and is considered investigational for all indications.", Description, Key Points, Key Words, Practice Guidelines, Governing Bodies, Coding and References.
Medical Policy Panel, July 2017
Medical Policy Group, August 2017 **(6):** Correction to description of recently cleared devices in Regulatory Status section. "Wireless injectable" removed from policy statement on dorsal root ganglion neurostimulation; Updates to Description, Key Points, and Governing Bodies.
Medical Policy Panel, April 2018
Medical Policy Group, May 2018 **(6)**: Updates to Description, Key Points and References.
