

07.01.78 Implantable Peripheral Nerve Stimulation and Restorative Neurostimulation for the Treatment of Chronic Pain

Original Effective Date: October 2018

Review Date: August 2026

Revised: August 2026

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Related Policies:

- [01.01.32 Electrical and Electromagnetic Stimulation for the Treatment of Arthritis](#)
- [01.01.33 Cranial Electrotherapy Stimulation and Auricular Electrostimulation](#)
- [01.01.34 Interferential Current Stimulation](#)
- [01.01.35 Non-Implantable Percutaneous Electrical Nerve Stimulation and Percutaneous Neuromodulation Therapy](#)
- [01.01.36 Percutaneous Electrical Nerve Field Stimulation for Irritable Bowel Syndrome](#)
- [01.01.37 Miscellaneous Electrical Stimulation for the Treatment of Pain](#)
- [07.01.61 Spinal Cord and Dorsal Root Ganglion Stimulation](#)
- [07.01.70 Peripheral Subcutaneous Field Stimulation \(PSFS\)](#)

Summary

Description

Implantable Peripheral Nerve Stimulation

Implantable peripheral nerve stimulation (PNS) is a percutaneous system consisting of leads, electrodes, and pulse transmitter that delivers electrical impulses to peripheral nerves. Leads are placed using ultrasound and/or fluoroscopic guidance and can be placed for temporary or permanent use in an outpatient procedure. PNS has been evaluated across a range of chronic pain conditions amenable to stimulation at a peripheral nerve target, including peripheral neuropathic pain of the extremities, post-amputation and phantom-limb pain, persistent post-surgical pain, axial low back pain (including persistent spinal pain syndrome [PSPS]), and craniofacial pain.

Restorative Neurostimulation

Restorative neurostimulation is a minimally invasive method of innervating the multifidus muscle of the lower back to override the cycle of lumbar multifidus muscle degeneration. It is intended to be used as a rehabilitative therapy for individuals with impaired neuromuscular control associated with mechanical chronic low back pain (CLBP). After the neurostimulation device is implanted, isolated electrical impulses causing controlled muscle contractions by way of self-anchoring leads is provided directly to nerves responsible for these muscles (L2 medial branch of the dorsal ramus as it crosses the transverse process at L3). This device is thought to relieve intractable CLBP and helps retrain the low back muscles to strengthen again on their own.

Summary of Evidence

Implantable Peripheral Nerve Stimulation

For individuals who have peripheral neuropathic chronic pain who receive implantable peripheral nerve stimulation (PNS), the evidence includes two randomized controlled trials (RCTs) and several systematic reviews. Relevant outcomes are symptoms, medication use, and quality of life (QOL). Both RCTs favored active PNS: responder rates were significantly higher with PNS than in the (38% vs/ 10% using a $\geq 30\%$ pain-reduction threshold in one trial and 84% vs 3% using a $\geq 50\%$ threshold in the other), with concordant improvements in quality of life and the Patient Global Impression of Change and response sustained through 12 months in the larger trial; no serious adverse events were reported. The systematic reviews were directionally consistent but graded the certainty of evidence as low to very low, reflecting predominantly observational source data and substantial heterogeneity. Limitations include small sample sizes, heterogeneous patient populations, differing responder definitions across trials, high attrition after randomization, and an open-label, usual care comparator with a short (3-month) controlled period before crossover in the pivotal trial. Additional evidence from adequately powered, blinded RCTs with longer durations of comparative data are necessary to assess the efficacy and durability of implantable PNS. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have chronic post-amputation pain (including residual-limb and phantom-limb pain) who receive temporary (60-day) peripheral nerve stimulation (PNS), the evidence includes a single small, sham-controlled RCT with 12-month follow-up. Relevant outcomes are symptoms, medication use, and quality of life. Responder rates ($\geq 50\%$ pain reduction) were significantly higher with active PNS than with sham (58% to 67% vs. 14%), and the between-group difference persisted at 12 months; no serious

adverse events were reported. Limitations include a very small sample size, a partial-crossover design that limited the duration of time-matched placebo comparison, and optional, inconsistently applied lead replacement at crossover. Additional evidence from adequately powered RCTs with longer time-matched comparative follow-up is necessary to assess the efficacy and durability of PNS. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have persistent post-surgical pain who receive temporary (14- to 60-day) PNS, the evidence includes two small, sham-controlled RCTs. Relevant outcomes are symptoms, medication use, function, and quality of life. Both trials favored active PNS, with significantly lower opioid consumption and pain scores in one, and a higher $\geq 50\%$ pain-relief responder rate (60% vs. 24%) with concordant functional and quality-of-life gains in the other; no serious adverse events were reported. Limitations include small sample sizes, short controlled treatment durations, high loss to follow-up, early termination of one trial owing to COVID-19-related enrollment challenges, and heterogeneous surgical populations. Additional evidence from RCTs with larger sample sizes and longer durations of comparative data is necessary to assess the efficacy and durability of PNS. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have chronic axial low back pain, including persistent spinal pain syndrome, who receive temporary or permanent PNS, the evidence includes two RCTs: one large, pragmatic trial with an open-label usual-care comparator and one small, sham-controlled trial. Relevant outcomes are symptoms, medication use, disability, and quality of life. Responder rates ($\geq 50\%$ pain reduction) were significantly higher with PNS than with the comparator (55% vs. 26% and 63% vs. 16%), with concordant improvements in disability, PGIC, and quality of life. Limitations include the open-label, unblinded comparator in the larger trial; the very small sample size and short (1-month) blinded window in the sham-controlled trial, with long-term data drawn from its uncontrolled active arm; and heterogeneity in device modality and stimulation target. Additional evidence from adequately powered, blinded RCTs with longer comparative follow-up is necessary to assess the efficacy and durability of PNS. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have refractory chronic craniofacial neuropathic pain who receive permanent PNS, the evidence includes a single RCT that used an enriched-enrollment, randomized-withdrawal design. Relevant outcomes are symptoms, medication use, and quality of life. Among early responders randomized to continued stimulation versus device deactivation, 69% versus 11% achieved $\geq 50\%$ pain relief at 3 months (60% vs. 10% in the intention-to-treat analysis), with concordant secondary gains and no serious adverse events. Limitations include the single-trial evidence base, an enriched-enrollment design that restricts randomization to early responders and may overstate the effect relative to an all-comers population, and a short (3-month) blinded withdrawal window. Additional evidence from independent RCTs with all-comers enrollment and longer comparative follow-up is necessary to assess the efficacy and durability of PNS. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Restorative Neurostimulation

For individuals who have chronic pain conditions including low back pain who receive restorative neurostimulation therapy (ReActiv8), the evidence includes a systematic review, 1 sham-controlled RCT (N = 204), 1 open-label RCT (N=203), 1 prospective single-arm trial (N = 53), and a case series (N = 44). Relevant outcomes are symptoms, functional outcomes, quality of life (QOL), and medication use. In the sham-controlled RCT, there was no difference between groups on the primary endpoint of treatment response at 120 days, defined as the composite of 30% or greater reduction in VAS and no increase in pain medications (57.1% intervention vs 46.6% sham; $p = .1377$). Prespecified secondary analyses of

primary outcome data favored the intervention group, but clinical significance is unclear. A post-hoc reanalysis of the sham-controlled RCT using common clinically relevant thresholds reported statistically significant differences favoring treatment for disability, quality of life, and patient satisfaction, but not for categorical pain responder rates. The outcome thresholds evaluated were not included in the original trial's prespecified analysis plan. An uncontrolled follow-up phase of the RCT reported continued improvement in pain scores through 3 years but results are at high risk of bias due to lack of a control group and high attrition. Nonrandomized studies are limited by lack of blinding, no sham control, high attrition, and small sample sizes. The open-label RCT showed statistically significant improvements in the treatment arm compared to the control arm in the primary and secondary outcomes. However, limitations included lack of blinding, imbalance in baseline depression between treatment and control arms, and greater clinical contact than standard management protocols in the treatment arm. Nonrandomized studies are limited by lack of blinding, no sham control, high attrition, and small sample sizes. Additional evidence from longer-term sham controlled RCTs is needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information

Not applicable.

OBJECTIVE

The objective of this evidence review is to 1) Determine whether the use of implantable peripheral nerve stimulation improves the net health outcome in individuals with chronic pain conditions by stimulation of the peripheral nerves, including peripheral neuropathic (extremity), post-amputation/phantom-limb, persistent post-surgical, axial low back (including persistent spinal pain syndrome), and craniofacial pain; and 2) Determine whether restorative neurostimulation improves the net health outcome in individuals with chronic pain conditions including but not limited to chronic low back pain (CLBP).

PRIOR APPROVAL

Not applicable.

POLICY

Implantable peripheral nerve stimulation (PNS) (see [Regulatory Status](#)) is considered **investigational** as a treatment for chronic pain of peripheral nerve origin, including but not limited to the following indications because the evidence is insufficient to determine the effects of this technology on net health outcomes:

- Axial low back pain (including persistent spinal pain syndrome [PSPS])
- Craniofacial pain
- Peripheral neuropathic pain of the upper and lower extremities
- Persistent post-surgical pain
- Post-amputation/phantom-limb pain

Restorative neurostimulation (ReActiv8) for the management of chronic pain including but not limited to chronic low back pain (CLBP) is considered **investigational** because the evidence is insufficient to determine the effects of this technology on net health outcomes.

POLICY GUIDELINES

Spinal Cord and Dorsal Root Ganglion Stimulation are covered in policy [07.01.61](#) and are not reviewed herein.

The Nalu Medical, Inc. and Neuspera Medical Inc. device indications state "trial devices are solely for trial stimulation (no longer than 30 days) to determine efficacy before recommendation for a permanent (long term) device."

Persistent Spinal Pain Syndrome (PSPS)

- Type 1: No prior spine surgery
- Type 2: Persistent or recurrent pain after spin surgery, previously termed failed back surgery syndrome) that is refractory to conservative management.

Coding

See the [Codes](#) table for details.

BACKGROUND

Chronic Pain Conditions

Chronic, noncancer pain is responsible for a high burden of illness and can be a high burden of illness and can be defined as persistent pain that lasts for more than 3-months. Peripheral nerve stimulation has been evaluated across a range of chronic pain conditions amenable to stimulation at a peripheral nerve target, including peripheral neuropathic pain of the extremities, post-amputation and phantom-limb pain, persistent post-surgical pain, axial/low back pain (including persistent spinal pain syndrome [PSPS]), and craniofacial pain. The clinical context and therapy rationale specific to each indication are described in the corresponding sections of the review below.

Chronic Musculoskeletal Pain

A variety of chronic musculoskeletal pain conditions including but not limited to chronic low back pain (CLBP) present a substantial burden to individuals, adversely affecting function and QOL.

Treatment

Treatments for chronic pain include exercise, physical therapy and topical, oral and injectable medications. A variety of electrical stimulation devices are available to treat pain. Many of these are surface or percutaneous devices, but some are temporarily and permanently implanted. Implanted devices have potential safety issues such as adverse effects associated with the implantation process, device-related pain and lead migration. *See Related Policies above for additional electrical stimulation medical policies for the treatment of pain.*

Implantable Peripheral Nerve Stimulation

StimRouter is implanted during a minimally invasive outpatient procedure using local anesthesia. There is no implanted pulse generator as the StimRouter electric field conductor resides outside the body. A small lead is implanted. The E-EFC delivers electrical signs through the skin to the implanted StimRouter lead. The E-EFC can store up to eight custom stimulation programs. The E-EFC attaches into the disposable user patch, transmitting stimulation through the patch's gel electrodes. After implant procedure and initial programming, the individual manages their symptoms by using a wireless external programmer. The StimRouter Neuromodulation System is indicated for pain management in adults who have severe intractable chronic pain of peripheral nerve origin, as an adjunct to other modes of therapy (e.g., medications). The StimRouter is not intended to treat pain in the craniofacial region.

SPRINT PNS System is implanted for up to 60 days in the back and/or extremities for symptomatic relief of chronic, intractable pain, post-surgical and post-traumatic acute pain; symptomatic relief of post-traumatic pain; symptomatic relief of post-operative pain. The SPRINT PNS System is not intended to treat pain in the craniofacial region. The system consists of a percutaneous electrode placed using an introducer needle near a target peripheral nerve and an external pulse generator that delivers stimulation to the percutaneous electrode.

Nalu Neurostimulation implanted and sends pulsed electrical current to inhibit the transmission of pain signals. The device comprises 5 components including a micro-implantable pulse generator, which is battery free and powered by an externally worn therapy disc. The electrical pulses are delivered through implantable leads (4 or 8 cylindrical electrodes), which are controlled by therapy disc. Leads are implanted in peripheral nerve areas. This system is indicated for pain management in adults who have severe intractable chronic pain of peripheral nerve origin but is not intended to treat pain in the craniofacial region.

Freedom PNS system is indicated for pain management for individuals with severe intractable chronic pain of peripheral nerve origin (targeted areas include trunk, lower back, shoulder, arms, hands, knees, foot/ankle as well as craniofacial). The device comprises of 4 to 8 lead/electrodes placed near the affected peripheral nerve via minimally invasive percutaneous approach. The Freedom Trial Lead Kit is only to be used in conjunction with the Freedom Neurostimulator Kit. The trial devices are solely used for a trial stimulation period (no longer than 30 days) to determine the efficacy before recommendation for permanent placement.

TalisMann Neuromodulation System is indicated for pain management in individuals who have severe intractable chronic pain of peripheral nerve origin (not intended to treat pain in the craniofacial region). This system has 4 lead/electrodes placed near the affected peripheral nerve via minimally invasive percutaneous approach. Patients undergo a temporary trial (up to 30 days) to determine efficacy prior to permanent placement.

Restorative Neuromodulation Therapy

Restorative neuromodulation therapy (ReActiv8) uses an implanted device to deliver electrical stimulation to the nerves controlling the multifidus muscles of the lumbar spine. It is proposed that restorative neuromodulation reduces pain by triggering contractions of the multifidus muscles to restore neuromuscular control and help stabilize the spine. It is intended for individuals with intractable chronic low back pain associated with multifidus dysfunction for whom available low back pain treatments do not provide sufficient or durable symptom relief.

Regulatory Status

In 2020, the ReActiv8 (Mainstay Medical) was FDA approved through the Premarket Approval (PMA) process (PMA P190021) for individuals with intractable mechanical chronic low back pain associated with multifidus dysfunction for whom available low back pain treatments do not provide sufficient or durable symptom relief.

A number of PNS devices have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. These are listed in Table 1.

Two PNS devices by Stimwave Technologies Inc., the StimQ Peripheral Nerve Stimulator (PNS) System and the Receiver Kit, Trial Kit, Spare Lead Kit, Sterile Revision Kit, SWAG Kit, SWAG Accessory Kit, Charger Kit, were recalled in Sept 2020 for the product containing a non-functional component not referenced in product labeling.

Table 1. FDA-Cleared Peripheral Nerve Stimulation Devices (FDA Product Codes: GZF, NHI)

Device Name	Manufacturer	Cleared	510(k)	Indications
SPRINT Peripheral Nerve Stimulation System	SPR Therapeutics, Inc.	July 2018	K181422	The SPRINT Peripheral Nerve Stimulation (PNS) System is indicated for up to 60 days in the back and/or extremities for: Symptomatic relief of chronic, intractable pain, post-surgical and post-traumatic acute pain; Symptomatic relief of post-traumatic pain; Symptomatic relief of post-operative pain. The SPRINT PNS System is not intended to treat pain in the craniofacial region.
Nalu Neurostimulation Kit (Integrated, 40 cm: Single 8/Dual 8), Nalu Neurostimulation Kit (Ported, 2 cm: Single 8/Dual 8), Dual 8 Ported Nalu Implantable Pulse Generator with 40 cm Kit, 40 cm/ 60 cm Trial/Extension Lead Kits, Patient Kits and miscellaneous replacement kits	Nalu Medical, Inc.	March 2019	K183579	This system is indicated for pain management in adults who have severe intractable chronic pain of peripheral nerve origin, as the sole mitigating agent or as an adjunct to other modes of therapy used in a multidisciplinary approach. The system is not intended to treat pain in the craniofacial region.
IPG, integrated, 25/40 cm, single, tined, IPG, 2 cm, single 4, Lead (25/40 cm, 4, tined), Extension - 4	Nalu Medical, Inc.	Sept 2019	K191435	This system is indicated for pain management in adults who have severe intractable chronic pain of peripheral nerve origin, as the sole mitigating agent, or as an adjunct to other modes of therapy used in a multidisciplinary approach. The system is not intended to treat pain in the craniofacial region.
StimRouter Neuromodulation System	Bioness, Inc.	Oct 2019, March	K190047, K200482, K211965	The StimRouter Neuromodulation System is indicated for pain management in adults who have severe

Device Name	Manufacturer	Cleared	510(k)	Indications
		2020, Feb 2022		intractable chronic pain of peripheral nerve origin, as an adjunct to other modes of therapy (e.g., medications). The StimRouter is not intended to treat pain in the craniofacial region.
Stimulator, Stimulator Kit, External Transmitter, External Transmitter Kit (StimQ)	Micron Medical Corporation	Aug 2020	K200848	Moventis PNS is indicated for pain management in adults who have severe intractable chronic pain of peripheral nerve origin, as the sole mitigating agent, or as an adjunct to other modes of therapy used in a multidisciplinary approach. The Moventis PNS is not intended to treat pain in the craniofacial region.
Neuspera Neurostimulation System (NNS)	Neuspera Medical, Inc.	Aug 2021	K202781	The Neuspera Neurostimulation System (NNS) is indicated for pain management in adults who have severe intractable chronic pain of peripheral nerve origin, as the sole mitigating agent or as an adjunct to other modes of therapy used in a multidisciplinary approach. The system is not intended to treat pain in the craniofacial region.
Neuspera Nuity System	Neuspera Medical, Inc.	April 2023	K221303	The Neuspera Nuity™ System (NNS) is indicated for pain management in adults who have severe intractable chronic pain of peripheral nerve origin, as the sole mitigating agent or as an adjunct to other modes of therapy used in a multidisciplinary approach. The system is not intended to treat pain in the craniofacial region.
Freedom Peripheral Nerve Stimulator (PNS) System	Curonix, LLC	June 2024	K233162	The Freedom Peripheral Nerve Stimulator (PNS) System is indicated for pain management in adults who have severe intractable chronic pain of peripheral nerve origin, as the sole mitigating agent, or as an adjunct to other modes of therapy used in a multidisciplinary approach. The Freedom Trial Lead Kit is only to be used in conjunction with the Freedom Neurostimulator Kit. The trial devices are solely used for a trial stimulation period (no longer than 30 days) to determine efficacy before recommendation for a permanent (long term) device.

Device Name	Manufacturer	Cleared	510(k)	Indications
Nalu Neurostimulation Kit (Integrated 40 cm: Single 8/Dual 8), Nalu Neurostimulation Kit (Ported, 2 cm: Single 8/Dual 8), Dual 8 Ported Nalu Implantable Pulse Generator with 40 cm Kit, 40 cm/60 cm/60 cm Trial/Extension Lead Kits, Patient Kits and Miscellaneous Replacement Kits	Nalu Medical, Inc.	Aug 2024	K232415	This system is indicated for pain management in adults who have severe intractable chronic pain of peripheral nerve origin, as the sole mitigating agent, or as an adjunct to other modes of therapy used in a multidisciplinary approach. The system is not intended to treat pain in the craniofacial region. The trial devices are solely used for trial stimulation (no longer than 30 days) to determine efficacy before recommendation for a permanent (long term) device.
TalisMann Neuromodulation System	Bioventus, LLC	July 2025	K243678	The TalisMann Neuromodulation System is indicated for pain management in adults who have severe intractable chronic pain of peripheral nerve origin, as an adjunct to other modes of therapy (eg, medications). The TalisMann Neuromodulation System is not intended to treat pain in the craniofacial region.

RATIONALE

This evidence review was created in October 2018 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through August 2026.

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 individuals 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 1 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.

Implantable Peripheral Nerve Stimulation

Chronic Peripheral Neuropathic Pain

Clinical Context and Therapy Purpose

The purpose of implantable PNS in individuals who have chronic pain of peripheral nerve origin is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population(s) of interest is individuals with chronic pain of peripheral nerve origin which may be caused by damage to the peripheral nerves impacting the upper and lower extremities that is persistent for longer than 3 months.

Interventions

The therapy being considered is implantable PNS. It is a percutaneous systems consisting of leads, electrodes, and a pulse transmitter that delivers electrical impulses to the peripheral nerves. Leads are placed with ultrasound guidance and can be placed for temporary or permanent use in an outpatient procedure.

Comparators

The following therapies are currently being used to make decisions about implantable PNS: pharmacologic and nonpharmacologic treatments.

Outcomes

The general outcomes of interest are symptoms, medication use, and QOL.

As a chronic condition, follow-up of at least 6 weeks to 12 months would be desirable to assess outcomes in chronic neuropathic pain.

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommends that chronic pain trials should consider assessing outcomes representing 6 core domains: pain, physical functioning, emotional functioning, participant ratings of improvement and satisfaction with treatment, symptoms and adverse events, and participant disposition. Table 2 summarizes provisional benchmarks for interpreting changes in chronic pain clinical trial outcome measures per IMMPACT.

Table 2. Health Outcome Measures Relevant to Individuals with Chronic Pain

Outcome	Measure (Units)	Description	Thresholds for Improvement/Decline or Clinically Meaningful Difference (If Known)
Pain intensity	0 to 10 numeric rating scale	Patient reported rating of pain intensity.	Minimally important (10 to 20% decrease) Moderately important ($\geq 30\%$ decrease) Substantial ($\geq 50\%$ decrease)
Physical functioning	Multidimensional Pain Inventory Interference Scale	A 60-item self-report inventory of patients' cognitive, behavioral, and affective responses to their condition. Decreasing score indicates improvement.	Clinically important (≥ 0.6 point decrease)
	Brief Pain Inventory Interference Scale	A 7-item self-report assessment of pain interference with physical and emotional functioning and sleep. Decreasing score indicates improvement.	Minimally important (1 point decrease)
Emotional functioning	Beck Depression Inventory (score)	Assessment of depression severity ranging from 0 to 63. Decreasing score indicates improvement.	Clinically important (≥ 5 point decrease)
Profile of Mood States	Total Mood Disturbance (score)	A 65-item checklist of mood disturbances with 6 subscale scores. Decreasing score indicates improvement.	Clinically important (≥ 10 to 15 point decrease)
	Specific Subscales (score)		Clinically important (≥ 2 to 12 point change)
Global Rating of Improvement	Patient Global Impression of Change (rating)	A single-item rating by participants of their response to treatment in a clinical trial using a 7-point rating scale, ranging from "very much improved" to "very much worse."	Minimally important: "minimally improved" Moderately important: "much improved" Substantial: "very much improved"

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Char et al (2022) conducted a systematic review evaluating 14 prospective studies (3 RCTs) on the efficacy of implantable PNS for peripheral neuropathic pain. A majority of the studies included were case

series or open-label studies. Meta-analyses were not performed. The review found moderate-quality evidence for phantom limb pain and low-quality evidence for other conditions such as complex regional pain syndrome, shoulder pain, post-surgical pain, and mononeuropathies. Limitations included high heterogeneity across studies, small sample sizes, short follow-up durations, lack of control groups in many studies, and potential attrition bias. Additionally, several studies only analyzed patients who responded positively to PNS, which may overestimate efficacy. The authors noted the need for more robust, well-powered RCTs to confirm study findings and better understand long-term outcomes

D'Souza et al. (2025) conducted a systematic review and random-effects meta-analysis of implantable PNS for chronic pain, pooling 106 studies (9,272 patients; 7 RCTs, 35 prospective and 64 retrospective observational studies) and reporting large reductions in pain intensity versus baseline at 3, 6, 12, and 24 months (Hedges' g 2.92, 3.08, 2.68, and 2.08 respectively; all $p < .001$). At the pre-specified 6-month primary timepoint the pooled g was 3.08 (95% CI 2.68–3.48) across 46 studies, with high statistical heterogeneity ($I^2=91\%$). GRADE certainty was rated LOW at 3, 6, and 24 months and VERY LOW at 12 months, reflecting predominantly observational source data, risk of bias, substantial heterogeneity, and evidence of small-study effects (LFK 5.55). Effect magnitude varied markedly by anatomical site (pelvis g 4.86 to trunk g 1.61), and no difference was seen between temporary and permanent devices.

Manchikanti et al. (2025) is a PRISMA systematic review and meta-analysis restricted to RCTs of PNS for chronic pain. From 27 RCT publications the authors included 9 trials (Cochrane: 7 high- and 2 moderate-quality; IPM-QRB: all 9 moderate; GRADE: 7 moderate, 2 low) and concluded there is fair (Level III) evidence with moderate certainty and a moderate strength of recommendation for implantable PNS following a successful trial (and for selective lumbar medial branch stimulation without a trial) and for 60-day temporary PNS. Quantitative pooling was limited by outcome-measure heterogeneity (I^2 up to 99% on two-trial pools). Conclusions were based on qualitative best-evidence synthesis plus GRADE rather than the pooled estimates.

Randomized Controlled Trials

StimRouter Neuromodulation System

Deer et al (2016) conducted an RCT to assess the safety and efficacy of PNS using the StimRouter Neuromodulation System to treat individuals with chronic pain of peripheral nerve origin. Participants (N=94) were randomized 1:1 into the treatment (n=45) or control (n=49) group. The treatment group received PNS and a stable dose of pain medications, and the control group received no PNS and a stable dose of pain medications for 90 days. After 90 days, crossover from the control group to the treatment group was offered. Study visits were planned at 30, 60, and 90 days after randomization, with follow-up at 6 and 12 months. The primary outcomes were pain relief and safety. Average pain at rest was measured by a numerical rating scale (NRS) over 3 months and safety was assessed by adverse events reported during the 1-year study period. A responder was defined as having at least a 30% decrease in the NRS with no upward titration in pain medications. Secondary outcomes included changes in medication, quality of life, patient global impression of change scale (PGIC), and change in worst pain using the NRS. At 90 days, there was a statistically significant difference between the treatment group and control group in the mean reduction in average pain from baseline (27.2% vs. 2.3%; $p < .0001$). There were statistically significantly more responders in the treatment group compared to the control group (38% vs. 10%; $p = .0048$). At 90 days, the treatment group compared to the control group had a significantly better improvement in quality of life (change from baseline [mean $\pm$ SD]: 1.4 ± 5.9 vs. -0.2 ± 3.4 ; $p = .037$) and PGIC (mean $\pm$ SD: 4.8 ± 1.5 vs. 2.5 ± 1.9 ; $p < .0001$). There was no device related serious adverse events through follow-up (mean duration: 320 days). Study characteristics and results are summarized in Tables 3 and 4. Study limitations are summarized in Tables 5 and 6.

Nalu Neurostimulation System

Engle et al (2025) reported the results of the COMFORT 2 (N=173) confirmatory randomized controlled trial (RCT) evaluating the safety and efficacy of peripheral nerve stimulation (PNS) using the Nalu Neurostimulation System for treating chronic peripheral neuropathic pain. The protocol for this study is identical to its sister study (COMFORT RCT, Hatheway et al 2024 below) to allow for pooling data from both trials. Patients were randomized to receive either PNS with conventional medical management (CMM) (n=109) or CMM alone (64) in a 2:1 ratio. Areas treated were limited to the shoulder, lower back, knee or the foot/ankle. The distribution of targeted areas of pain was as follows: low back (45.1%, 78/173), knee (22.5 %, 39/173), shoulder (14.5%, 25/173), foot/ankle (17.9%, 31/173). At 3 months the COMFORT 2 Active Arm responder rate (those who achieved $\geq 50\%$ pain reduction) was 80% (67/84) with an average pain reduction of 66%, compared to the Control Arm responder rate of 4% and average pain reduction of 3% ($p < 0.001$). The high responder rate (those who achieved $\geq 80\%$ pain reduction) was 30% (25/84) in the Active Arm compared to 0% in the Control Arm. At 6-months the Active Arm responder rate was 79% (64/81) with an average pain reduction of 64%; the high responder rate was 30% (24/81). No serious adverse events were reported. The pooled analysis COMFORT and COMFORT 2 data yielded a sample size of 250 (Active n=155; Control n=95). At 3 months the pooled Active Arm responder rate was 81% (103/127) with an average pain reduction of 66%, compared to the pooled Control Arm responder rate of 4% and an average pain reduction of 4% ($p < 0.001$); the high responder rate (those who achieved $\geq 80\%$ pain reduction) was 30% (38/127) for the pooled Active Arm compared to 1% in the pooled Control Arm. At 6 months the pooled Active responder rate was 82% (101/123) with an average pain reduction of 66%; the high responder rate was 33% (40/123). Study limitations included lack of blinding, small sample sizes, heterogeneous patient populations, high attrition rates and lack of long-term follow-up data. COMFORT 2 is an ongoing study and “authors will report additional data as it becomes available.” Engel et al (2026) reported the 24-month results of the ongoing COMFORT2 multicenter, post-market RCT using the Nalu Neurostimulation System for treating chronic peripheral neuropathic pain. The responder rate at 24 months was 85%, and it was 82% at 18 months. The average pain reduction as compared to baseline pain scores was 67% at 24 months (7.5 ± 1.2 to 2.4 ± 1.7 ; $p < 0.001$) and 65% at 18 months (7.5 ± 1.2 to 2.6 ± 1.7 ; $p < 0.001$). No adverse events were reported. A study limitation included only 46 of the original modified intent-to-treat (mITT) population (68%) were included in the 24-month analysis. The COMFORT2 is an ongoing study and the “authors will report additional results as they become available.”

Hatheway et al (2024) conducted a multicenter RCT evaluating the safety and efficacy of PNS using the Nalu Neurostimulation System for treating chronic peripheral neuropathic pain (COMFORT Study) (N=131). Patients were randomized to receive either PNS with conventional medical management (CMM) (n=58) or CMM alone (n=31), with 46 and 31 subjects respectively included in the modified intention-to-treat population. At 3 months, the responder rate ($\geq 50\%$ pain reduction) in the PNS with CMM arm compared to the CMM alone arm was statistically significantly higher (84% vs. 3%; $p < .001$) and as well as the pain reduction (67% vs. 6%; $p < .001$). These results were sustained at 6 months, with an 88% responder rate and 70% pain reduction in the PNS with CMM arm. There were no serious adverse events. Limitations included the lack of blinding, the short 3-month duration of the control arm, a disproportionate number of female participants (70%), and high attrition after randomization. Study characteristics and results are summarized in Tables 3 and 4. Study limitations are summarized in Tables 5 and 6.

Hatheway et al (2024) reported the 12-month results of the COMFORT Study. Patients from the CMM alone arm were given the option to cross over to the PNS with CMM arm after the initial 3 months. At 12 months, 87% of participants (53/61) were responders ($\geq 50\%$ pain reduction) with a mean pain score reduction from 7.5 ± 1.2 to 2.3 ± 1.7 ($p < .001$). High responders ($\geq 80\%$ pain reduction) comprised 31% of the cohort. There were no serious adverse events. Limitations include the lack of blinding, a short control

arm duration (3 months), absence of standardized neuropathic pain questionnaires, variability in conventional medical management, and a high attrition after randomization. Study characteristics and results are summarized in Tables 3 and 4. Study limitations are summarized in Tables 5 and 6.

Table 3. Summary of Key Randomized Controlled Trials Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Treatment (n=45)	Control (n=49)
Deer et al (2016)	US	13	NR	Individuals with chronic pain of peripheral nerve origin.	PNS and a stable dose of pain medications for 90 days with up to 12 month follow-up (n=45).	No PNS and a stable dose of pain medications for 90 days, then option to crossover to treatment with up to 12 month follow-up (n=49).
Hatheway et al (2024)	US	20	2022 (ongoing)	Adults aged 18 to 80 with chronic (≥6 months), intractable peripheral neuropathic pain in the low back, shoulder, knee, or foot/ankle, who had not responded adequately to conventional medical management (CMM). Subjects were required to have a pain score ≥6 and stable pain medication use for at least 30 days prior to enrollment.	PNS+CMM arm received a trial implant of the Nalu Neurostimulation System. Those achieving ≥50% pain relief during the trial proceeded to permanent implantation and continued with CMM (n=58).	CMM-only arm continued with their existing medical management regimen. At 3 months, they had the option to cross over to the treatment arm if they met specific criteria (e.g., <50% pain reduction, investigator approval) (n=31).

CMM: conventional medical management; NR: not reported; PNS: peripheral nerve stimulation; US: United States.

Table 4. Summary of Key Randomized Controlled Trials Results

Study	Mean Pain Reduction from Baseline (%)	Responders (%)	Pain Medication Increased, n (%)	Quality of Life, mean ± SD			PGIC, mean ± SD
StimeRouter Neuromodulation System							
	3 Months	3 Months	3 Months	Baseline	3 Months	Change	3 Months
Deer et al (2016)	N=94	N=94	N=94	N=94	N=94	N=94	N=94

Study	Mean Pain Reduction from Baseline (%)		Responders (%)		Pain Medication Increased, n (%)	Quality of Life, mean $\pm$ SD			PGIC, mean $\pm$ SD	
Treatment (n=45)	27.2		38		1 (2.2%)	35.5 $\pm$ 4.9	36.9 $\pm$ 4.5	1.4 $\pm$ 5.9	4.8 $\pm$ 1.5	
Control (n=49)	2.3		10		2 (4.1%)	36.0 $\pm$ 4.3	35.8 $\pm$ 4.3	-0.2 $\pm$ 3.4	2.5 $\pm$ 1.9	
p-value	<.0001		.0048		NR	.389	.250	.037	<.0001	
Nalu Neurostimulation System										
Hatheway et al (2024)	3 Months	6 Months	3 Months	6 Months						
Treatment (n=46)	67	70	84	88						
Control (n=31)	6	NA	3	NA						
p-value	<.001	NA	<.001	NA						
Hatheway et al (2024)	12 Months		12 Months							
Treatment (n=61)	69		87							
p-value	NR		NR							

NA: not applicable; NR: not reported; PGIC: patient global impression of change; RCT: randomized controlled trial; SD: standard deviation.

Table 5. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-up ^e
Deer et al (2016)	1. Population includes post-traumatic and post-surgical pain, which is not included in FDA approved device indications; 2. Types of pain medication not reported; Broad descriptions of pain sites; 4. Population is not representative of US diversity.			6. Clinically significant difference not supported.	1. Not sufficient duration for durability.

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-up ^e
Hatheway et al (2024)	5. Disproportionate number of female participants (70%).	5. Adjunct to conventional medical management, which was varied among participants and not clearly defined.	5. Cross-over design after initial 3 months.		
Hatheway et al (2024)					

US: United States.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5. Other.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 6. Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical ^f
Deer et al (2016)			1. Not registered on clinicaltrials.gov.	1. High loss to follow-up.		
Hatheway et al (2024)		1. Participants and study staff not blinded.		1. High loss to follow-up.		
Hatheway et al (2024)						

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.

^b Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.

^d Data Completeness key: 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); 7. Other.

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Nonrandomized Studies

Nonrandomized studies (Deer 2010, Oswald 2019, Langford 2023, Luna 2025) have been published but do not provide additional information on safety, efficacy, or subgroups beyond what is available in the RCTs and will not be reviewed in detail here.

Section Summary: Implantable Peripheral Nerve Stimulation for Chronic Peripheral Neuropathic Pain

The evidence for PNS in individuals with peripheral neuropathic chronic pain includes two RCTs (Deer et al [2016]; N=94; StimRouter; and Hatheway et al [2024], the COMFORT trial; N=131; Nalu) and several systematic reviews. Relevant outcomes are symptoms, medication use, and quality of life. Both RCTs favored active PNS: Deer reported a higher responder rate ($\geq 30\%$ pain reduction without increased medication) at 90 days (38% vs. 10%), with concordant gains in quality of life and PGIC, and COMFORT reported a $\geq 50\%$ pain-relief responder rate of 84% versus 3% at 3 months, sustained at 6 months (88%) and 12 months (87% following control-arm crossover); no serious adverse events were reported in either trial. The systematic reviews were consistent in direction but rated the certainty of evidence as low to very low, reflecting predominantly observational source data and substantial heterogeneity. Limitations include small sample sizes, heterogeneous neuropathic pain populations, differing responder definitions across trials, high attrition after randomization, and, most notably for the COMFORT trial, an open-label, usual-care comparator and a short (3-month) controlled period before crossover, which preclude durable time-matched comparison. Additional evidence from adequately powered, blinded RCTs with longer comparative follow-up is needed to determine the effect of PNS on the net health outcome in this population.

Post-Amputation and Phantom-Limb Pain

Clinical Context and Therapy Purpose

The purpose of temporary (60-day) implantable percutaneous PNS in individuals who have chronic post-amputation pain, including residual (stump) limb pain and phantom-limb pain, is to provide a treatment option that is an alternative to or an improvement on existing pharmacologic and nonpharmacologic therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant populations of interest are individuals with chronic post-amputation pain, including residual (stump) limb pain and phantom-limb pain, that persists for longer than 3 months and is inadequately controlled by conservative management.

Interventions

The therapy being considered is temporary implantable PNS. A percutaneous lead is placed under ultrasound guidance adjacent to the femoral and/or sciatic nerve and connected to an external pulse transmitter for a fixed treatment period of up to 60 days, after which the lead is removed (e.g., SPRINT PNS System).

Comparators

The following therapies are currently being used to make decisions about temporary implantable PNS for post-amputation pain: pharmacologic treatment and nonpharmacologic treatment. In controlled trials, sham stimulation often serves as the comparator.

Outcomes

The general outcomes of interest are pain intensity (commonly reported as the proportion of participants achieving $\geq 50\%$ pain reduction), pain interference, medication (including opioid) use, and quality of life, including the Patient Global Impression of Change (PGIC). See Table 2 for an overview of health outcomes.

Follow-up from the end of the 8-week treatment period through 12 months is of interest to monitor outcomes, given that the therapeutic effect is intended to persist after lead removal.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Randomized Controlled Trials

SPRINT Peripheral Nerve Stimulation

Gilmore et al (2019) conducted a multicenter, randomized, double-blinded, placebo-controlled trial evaluating the efficacy of a 60-day PNS treatment using the SPRINT PNS System for chronic neuropathic postamputation pain in lower extremity amputees (N=28). Participants were randomized to active PNS (n=12) or sham stimulation (n=14). After the initial 4 weeks, the sham stimulation group was given the option to cross over to active PNS. There was a statistically significantly higher responder rate ($\geq 50\%$ pain reduction) in the active PNS group compared to the sham stimulation group at 4 weeks (58% vs 14%; $p=.037$) and at 8 weeks (67% vs. 14%; $p=.014$). There were 22 study-related events in 46% (13/28) of participants. The authors noted several limitations including the small sample size, partial crossover design limiting long-term placebo comparison, variability in opioid use, and optional lead replacement at crossover, which may have affected outcomes. Study characteristics and results are summarized in Tables 7 and 8. Study limitations are summarized in Tables 9 and 10.

Gilmore et al (2019) reported the 12-month results of their study to evaluate the long-term efficacy of a 60-day PNS treatment for chronic post-amputation pain. The active treatment group (Group 1) received 8 weeks of active PNS, while the sham group (Group 2) received 4 weeks of sham stimulation followed by 4 weeks of active PNS in a partial crossover design. After the 8-week treatment period, all leads were removed and both groups were followed monthly for up to 12 months post-initial implantation. At 12 months, the response rate of Group 1 was statistically significantly higher than that of Group 2 at the end of the initial 4-week placebo period (67% vs. 0%; $p=.001$). Additionally, 56% of the active group reported $\geq 50\%$ reductions in pain interference, with significant improvements in depression scores (BDI-II) and PGIC. No serious adverse events were reported. Limitations included the small sample size, optional and

inconsistently applied lead replacement in the sham group after crossover, lack of time-matched placebo comparisons, and potential bias from missing data imputation. Study characteristics and results are summarized in Tables 7 and 8. Study limitations are summarized in Tables 9 and 10.

Table 7. Summary of Key Randomized Controlled Trials Characteristics

Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Gilmore et al (2019)	US	6	2015-2018	Individuals who underwent traumatic lower extremity amputation and were experiencing chronic neuropathic pain.	Active PNS for 4 weeks, with an optional extension to 8 weeks (n=12).	Sham stimulation for 4 weeks, with cross-over to active PNS for an additional 4 weeks (n=14).

PNS: peripheral nerve stimulation; US: United States.

Table 8. Summary of Key Randomized Controlled Trials Results

Study	Responders (%)		PGIC, mean $\pm$ SD	
SPRINT Peripheral Nerve Stimulation System				
Gilmore et al (2019)	4 Weeks	8 Weeks (control crossed over to treatment)	4 Weeks	8 Weeks (control crossed over to treatment)
Treatment (n=12)	58	67	1.4 $\pm$ 1.1	2.2 $\pm$ 0.9
Control (n=14)	14	14	0.6 $\pm$ 1.3	1.3 $\pm$ 1.0
p-value	.037	.014	NS	<.01
Gilmore et al (2019)	12 Months		3 Months	12 Months
Treatment (n=9)	67		1.9 $\pm$ 0.9	1.8 $\pm$ 1.3
Control (n=14)	0 (at end of 4 weeks before cross-over)		1.0 $\pm$ 0.8	1.2 $\pm$ 1.5
p-value	.001		<.05	NS

NS: not significant; PGIC: patient global impression of change; SD: standard deviation.

Table 9. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-up ^e
Gilmore et al (2019)			5. Cross-over design after initial 4 weeks.		
Gilmore et al (2019)					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 10. Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical ^f
Gilmore et al (2019)				1. High loss to follow-up.		
Gilmore et al (2019)						

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4.

Inadequate control for selection bias; 5. Other.

^b Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.

^d Data Completeness key: 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); 7. Other.

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Section Summary: Post-Amputation and Phantom-Limb Pain

The evidence for temporary (60-day) PNS in individuals with chronic post-amputation pain includes a single small, multicenter, double-blind, sham-controlled RCT with a partial-crossover design and 12-month follow-up (Gilmore et al [2019]; N=28). Relevant outcomes are symptoms, medication use, and quality of life. A statistically significantly higher proportion of the active PNS group achieved ≥50% pain reduction compared with sham at 4 weeks (58% vs. 14%) and 8 weeks (67% vs. 14%), and the difference persisted at 12 months relative to the sham group's end-of-placebo response (67% vs. 0%); no serious adverse events were reported. Limitations include a very small sample size, a partial-crossover design that limits the duration of time-matched placebo comparison, optional and inconsistently applied lead replacement at crossover, and variability in concurrent opioid use. Additional evidence from adequately powered RCTs with longer time-matched comparative follow-up is needed to determine the effect of temporary PNS on the net health outcome in this population.

Post-Surgical Pain

Clinical Context and Therapy Purpose

The purpose of temporary implantable percutaneous PNS in individuals who have persistent post-surgical pain is to provide a treatment option that is an alternative to or an improvement on existing pharmacologic and nonpharmacologic therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant populations of interest are individuals with persistent post-surgical (postoperative) pain. For example, following total knee arthroplasty or ambulatory orthopedic surgery, that persists beyond the expected period of surgical healing.

Interventions

The therapy being considered is temporary implantable PNS. A percutaneous lead is placed under ultrasound guidance adjacent to the target peripheral nerve and connected to an external pulse transmitter for a fixed treatment period (14 to 60 days), after which the lead is removed (e.g., SPRINT PNS System).

Comparators

The following therapies are currently being used to make decisions about temporary PNS for post-surgical pain: pharmacologic treatment and nonpharmacologic treatment. In controlled trials, sham stimulation often serves as the comparator.

Outcomes

The general outcomes of interest are pain intensity (including the proportion achieving $\geq 50\%$ pain reduction), opioid and analgesic consumption, physical function (e.g., Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC], walking ability), quality of life, and the Patient Global Impression of Change (PGIC). See Table 2 for an overview of health outcomes.

Follow-up through the treatment period and for several weeks to months thereafter is of interest to monitor outcomes, given that the therapeutic effect is intended to persist after lead removal.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Randomized Controlled Trials

Ilfeld et al (2021) conducted a multicenter, randomized, double-masked, sham-controlled pilot study evaluating the efficacy of PNS using the SPRINT PNS System for postoperative pain management following ambulatory orthopedic surgeries (N=65). Patients were randomized to receive either active PNS (n=31) or sham stimulation (n=34) for 14 days postoperatively. The active PNS group show statistically significantly lower opioid consumption with a median of 5 mg (IQR: 0, 30) vs. 48 mg (IQR: 25, 90) in the sham group (ratio of geometric means: 0.20; 97.5% CI: 0.07 to 0.57; p<.001) and lower average pain scores 1.1 ± 1.1 vs. 3.1 ± 1.7 (mean difference: -1.8; 97.5% CI: -2.6 to -0.9; p<.001). A limitation of this study was the treatment duration was for 14 days postoperatively. A responder outcome was not provided, so no further summary of results are included below. Study characteristics are summarized in Table 11. Study limitations are summarized in Tables 13 and 14.

Goree et al (2024) conducted a multicenter, randomized, double-blind, placebo-controlled trial, evaluating the efficacy of a 60-day PNS treatment using the SPRINT PNS System for persistent postoperative pain following total knee arthroplasty (TKA) (N=52). Patients were randomized to receive active PNS (n=20) or sham stimulation (n=21). Results showed a significantly greater proportion of those receiving PNS achieved ≥50% pain relief during weeks 5 to 8 compared to placebo (60% vs. 24%; p=.028), with corresponding improvements in walking ability (+47% vs. -9%; p=.048) and function (The Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] total score improvement: 62% vs. 35%; p=.006). Quality of life also improved more in the PNS group, with 90% reporting benefit (PGIC ≥1) versus 55% in the placebo group (p=.031). The study reported no serious or unanticipated adverse events. Limitations included the small sample size, a high loss to follow-up, and early study termination due to COVID-19-related enrollment challenges. Study characteristics and results are summarized in Tables 11 and 12. Study limitations are summarized in Tables 13 and 14.

Table 11. Summary of Key Randomized Controlled Trials Characteristics

Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Ilfeld et al (2021)	US	7	2019-2020	Adult patients (≥18 years) scheduled for ambulatory orthopedic surgeries.	Active PNS for 14 days postoperatively (n=31).	Sham stimulation for 14 days postoperatively (n=34).
Goree et al (2024)	US	11	2020-2023	Adults (≥21 years) who had undergone primary unilateral total knee arthroplasty (TKA) and continued to experience moderate-to-severe persistent postoperative pain (≥5/10 on the Brief Pain Inventory) for at least six months post-surgery.	Active PNS for 60 days (n=20).	Sham stimulation for 60 days (n=21).

PNS: peripheral nerve stimulation; TKA: total knee arthroplasty; US: United States.

Table 12. Summary of Key Randomized Controlled Trials Results

Study	Mean Pain Reduction from Baseline (%)	Responders (%)
SPRINT Peripheral Nerve Stimulation System		
Goree et al (2024)	5 to 8 Weeks	5 to 8 Weeks
Treatment (n=20)	54	60
Control (n=21)	26	24
p-value	.0021	.028

CI: confidence interval; HR: hazard ratio; NNT: number needed to treat; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk.

Table 13. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-up ^e
Ilfeld et al (2021)					1. Not sufficient treatment duration for benefit (14 days).
Goree et al (2024)					1. Not sufficient treatment duration for durability. 3. Terminated early due to COVID-19-related enrollment challenges.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5. Other.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 14. Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical ^f
Ilfeld et al (2021)					1. Not sufficient treatment duration for benefit (14 days).	
Goree et al (2024)					1. Not sufficient treatment duration for durability. 3. Terminated early due to COVID-19-related enrollment challenges.	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4.

Inadequate control for selection bias; 5. Other.

^b Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.

^dData Completeness key: 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); 7. Other.

^ePower key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.

^fStatistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Section Summary: Post-Surgical Pain

The evidence for temporary PNS in individuals with persistent post-surgical pain includes two small, multicenter, double-blind, sham-controlled RCTs of the SPRINT system (Ilfeld et al [2021]; N=65; 14-day treatment; and Goree et al [2024]; N=52; 60-day treatment following total knee arthroplasty). Relevant outcomes are symptoms, medication use, function, and quality of life. Both trials favored active PNS: Ilfeld reported significantly lower opioid consumption and average pain scores through 14 days (a responder outcome was not reported), and Goree reported a higher $\geq 50\%$ pain-relief responder rate during weeks 5 to 8 (60% vs. 24%), with concordant improvements in function, walking ability, and PGIC and no serious adverse events. Limitations include small sample sizes, short controlled treatment durations, high loss to follow-up, early termination of the Goree trial owing to COVID-19-related enrollment challenges, and heterogeneity across surgical populations. Additional evidence from larger RCTs with longer comparative follow-up is needed to determine the effect of temporary PNS on the net health outcome in this population.

Axial Low Back Pain and Post-Spinal-Surgery Syndrome

Clinical Context and Therapy Purpose

The purpose of temporary or permanent implantable PNS in individuals who have chronic axial low back pain, including persistent spinal pain syndrome (PSPS), is to provide a treatment option that is an alternative to or an improvement on existing pharmacologic, nonpharmacologic, and interventional therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant populations of interest are individuals with chronic axial low back pain confined to the lumbar region, including persistent spinal pain syndrome Type 1 (no prior spine surgery) and Type 2 (persistent or recurrent pain after spine surgery, previously termed failed back surgery syndrome), that is refractory to conservative management.

Interventions

The therapy being considered is implantable PNS delivered either as temporary (60-day) percutaneous stimulation of the lumbar medial branches (e.g., SPRINT PNS System) or as permanent high-frequency stimulation of the proximal peripheral nerves (e.g., Freedom/Curonix system).

Comparators

The following therapies are currently being used to make decisions about PNS for axial low back pain: pharmacologic treatment, nonpharmacologic treatment, and standard interventional management (e.g., radiofrequency ablation, injections, physical therapy). In the controlled trials, physician-directed usual care and sham stimulation served as comparators.

Outcomes

The general outcomes of interest are pain intensity (including the proportion achieving $\geq 50\%$ pain reduction on the Brief Pain Inventory [BPI] or visual analog scale [VAS]), disability (Oswestry Disability Index [ODI]), the Patient Global Impression of Change (PGIC), quality of life (EQ-5D-5L), and analgesic use. See Table 2 for an overview of health outcomes.

Follow-up of at least 3 to 6 months, with longer-term data where available, is of interest to monitor the durability of outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Randomized Controlled Trials

McCormick et al. (2026), the RESET trial, is a prospective, multicenter (21 US sites), pragmatic RCT (222 in the Full Analysis Set; 112 PNS, 110 usual care) comparing 60-day percutaneous SPRINT PNS of the lumbar medial branches against physician-directed usual care with standard interventional management (RFA, injections, physical therapy) for refractory axial chronic low back pain confined to the lumbar region (radicular leg pain and prior lumbar spine surgery were excluded). Using sequential non-inferiority-then-superiority testing, 60-day PNS met its primary endpoint: 55% of PNS participants achieved $\geq 50\%$ reduction in average pain (BPI5) at 3 months versus 26% with usual care ($P < .001$), confirmed both non-inferior and superior. Benefits were concordant across secondary patient-centric outcomes: disability ($\geq 30\%$ ODI: 70% vs. 47%), pain interference, worst pain, PGIC, quality of life, and analgesic reduction (63% vs. 46%), and between-group differences remained statistically significant through 6 months. Because the pragmatic design used an active usual-care comparator, blinding was not possible after randomization and no sham control was included; the concurrent-controlled comparison extended only to 6 months, with crossover offered at 12 months. Study characteristics and results are summarized in Tables 15 and 16. Study limitations are summarized in Tables 17 and 18.

Billet et al. (2026), the PPNS study, is a prospective, double-blind, sham-controlled RCT conducted at 2 sites (39 enrolled; 38 completers, active n=19, sham n=19) of subthreshold high-frequency stimulation delivered bilaterally at the proximal peripheral nerves at T9 using the Freedom (Curonix) permanent system, for refractory chronic back pain in patients evenly split between PSPS Type 1 (no prior spine surgery) and Type 2 (post-surgical). All patients went directly to permanent implant without a trial phase. At the 1-month primary endpoint (per-protocol, n=38), the active arm's responder rate ($\geq 50\%$ relief or VAS ≤ 30 mm) was 63% versus 16% with sham ($P=.007$), with significant secondary gains in back-pain VAS, ODI, PGIC, and EQ-5D-5L; leg-pain reduction was not significant. The blinded comparison extended only to approximately 1 month: nonresponders were progressively unblinded and all sham participants had crossed to active stimulation by 3 months, so the reported longer-term results—including a mean 64% VAS reduction at 36 months (n=22)—derive from the uncontrolled active arm rather than a randomized comparison. Study characteristics and results are summarized in Tables 15 and 16. Study limitations are summarized in Tables 17 and 18.

Table 15. Summary of Key Randomized Controlled Trials Characteristics

Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
McCormick et al (2026); RESET	US	21	2020-2023	Refractory axial chronic low back pain ≥ 6 mo confined to the lumbar region (no extremity radiation); failed ≥ 2 prior therapies	60-day percutaneous SPRINT PNS of the lumbar medial branches (n=112)	Physician-directed usual care with standard interventional management (RFA, injections, PT); crossover offered at 12 mo (n=110)
Billet et al (2026); PPNS	Belgium	2	2018-2019 (36-month follow-up to 2022)	Refractory chronic back pain, PSPS Type 1 (no prior spine surgery) & Type 2 (post-surgical), 50/50 split; VAS ≥ 50 mm, ≥ 6 mo	Bilateral subthreshold high-frequency stimulation of proximal peripheral nerves at T9; Freedom (Curonix) permanent system, direct-to-permanent (n=19)	Sham (software blocks transmitter-implant communication); subthreshold design keeps patients & assessors blinded (n=19)

PNS: peripheral nerve stimulation; PSPS: persistent spinal pain syndrome; PT: physical therapy; RFA: radiofrequency ablation; US: United States; VAS: visual analog scale.

Table 16. Summary of Key Randomized Controlled Trials Results

Study	Responder Rate	Pain Reduction	ODI	PGIC	Quality of Life	Analgesic Reduction (%)
McCormick et al (2026); RESET	$\geq 50\%$ Pain Responders (%)	Mean Pain Reduction (%)	$\geq 30\%$ ODI Improvement (%)	PGIC $\geq$ “much improved” (%)	HRQoL (EQ-VAS), change in points	Analgesic Reduction (%)
60-day PNS (n=112)	55	51	70	62	+12	63

Study	Responder Rate	Pain Reduction		ODI	PGIC	Quality of Life	Analgesic Reduction (%)
Usual care (n=110)	26	24		47	29	+3	46
p-value	<.001	<.001		<.001	<.001	.022	.018
Billet et al (2026); PPNS	Responder Rate (%)	Back-pain Reduction (mean, mm)	Leg-pain Reduction (mean, mm)	ODI (point reduction)	PGIC (median category)	EQ-5D-5L, change	
Active (n=19)	63	34.9	12.4	15.4	5	+0.248	
Sham (n=19)	16	18.2	6.0	7.7	3	+0.083	
p-value	.007	.014	.33 (NS)	.046	.031	.011	

EQ-5D-5L: EuroQol 5-Dimension 5-Level; EQ-VAS: EuroQol visual analog scale; HRQoL: health-related quality of life; NS: not significant; ODI: Oswestry Disability Index; PGIC: patient global impression of change; PNS: peripheral nerve stimulation.

Table 17. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-up ^e
McCormick et al (2026); RESET			5. Open-label usual-care comparator (no sham).		1. Concurrent-controlled comparison limited to 6 months (crossover offered at 12 months).
Billet et al (2026); PPNS	2. Mixed PSPS Type 1 (no prior spine surgery) and Type 2 (post-surgical).	5. Direct-to-permanent implant, no trial phase (counter to trial-before-permanent coverage criteria).	5. Sham present only to ~1 month; nonresponders unblinded and all sham crossed over by 3 months.		1. Concurrent-controlled comparison limited to the 1-month endpoint; single-arm thereafter.

PSPS: persistent spinal pain syndrome.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5. Other.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 18. Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical ^f
McCormick et al (2026); RESET		1. Participants and study staff not blinded (open-label; blinding not possible post-randomization).		1. Missing data (179 of 222 completed the 3-month primary); imputed by predictive mean matching.		
Billet et al (2026); PPNS	4. Sponsor staff programmed devices and opened randomization.			1. High loss to follow-up (38 completers at 1 month; 22 at 36 months).		5. Hierarchical testing continued past a non-significant step (leg pain).

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.

^b Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.

^d Data Completeness key: 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); 7. Other.

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Section Summary: Axial Low Back Pain and Post-Spinal-Surgery Syndrome

The evidence for temporary or permanent PNS in individuals with chronic axial low back pain, including PSPS, includes two RCTs. Relevant outcomes are symptoms, medication use, disability, and quality of life. The RESET trial (McCormick et al [2026]) was a large, pragmatic, multicenter RCT (N=222) comparing 60-day temporary medial-branch PNS with physician-directed usual care; 55% of the PNS group achieved ≥50% pain reduction at 3 months versus 26% with usual care, with concordant improvements in disability, PGIC, quality of life, and analgesic reduction, and between-group differences remained statistically significant through 6 months. The PPNS study (Billet et al [2026]) was a small, double-blind, sham-controlled RCT (N=39) of permanent high-frequency stimulation; the active arm achieved a 63% responder rate versus 16% with sham at the 1-month primary endpoint, with significant gains in back-pain VAS, ODI, PGIC, and EQ-5D-5L (leg-pain reduction was not significant) and active-arm improvement reported as sustained through 36 months. Limitations include the open-label, unblinded usual-care comparator in RESET; the small sample size and short (1-month) blinded window in PPNS, with longer-term data drawn from the uncontrolled active arm; and heterogeneity in device modality (temporary vs. permanent) and stimulation target. Additional evidence from adequately powered, blinded RCTs with longer comparative follow-up is needed to determine the effect of PNS on the net health outcome in this population.

Craniofacial Pain

Clinical Context and Therapy Purpose

The purpose of permanent implantable PNS in individuals who have refractory chronic craniofacial neuropathic pain is to provide a treatment option that is an alternative to or an improvement on existing pharmacologic and nonpharmacologic therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest are individuals with refractory chronic craniofacial neuropathic pain in the trigeminal and/or occipital nerve distributions that persists for longer than 3 months and is inadequately controlled by conservative management.

Interventions

The therapy being considered is permanent implantable PNS using a high-frequency, electromagnetic-coupling system (Freedom/Curonix, cleared under K233162, which carries a craniofacial-inclusive labeled indication).

Comparators

The following therapies are currently being used to make decisions about permanent PNS for craniofacial pain: pharmacologic treatment and nonpharmacologic treatment. In controlled trials, sham stimulation often serves as the comparator.

Outcomes

The general outcomes of interest are pain intensity (including the proportion achieving $\geq 50\%$ pain reduction and VAS reduction), the Brief Pain Inventory–Facial (BPIF), the Patient Global Impression of Change (PGIC), and the short-form McGill Pain Questionnaire (MPQ-SF-2). See Table 2 for an overview of health outcomes.

Follow-up of at least 3 months, with longer-term data where available, is of interest to monitor the durability of outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.

- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Randomized Controlled Trials

Hayek et al. (2025), the CFPNS trial, is a multicenter (7 US sites) randomized controlled trial conducted under an FDA IDE of a high-frequency electromagnetic-coupling permanent PNS (Freedom/Curonix, K233162) for refractory chronic craniofacial neuropathic pain in trigeminal and occipital nerve distributions. It uses an enriched-enrollment randomized-withdrawal design: all 60 patients were permanently implanted, 56/60 (93%) responded during a 7-day assessment, and responders were then randomized to continued stimulation (active) or 3-month device deactivation (then reactivated). At the 3-month primary endpoint, 69% of the active arm versus 11% of the deactivated arm had $\geq 50\%$ pain relief ($P < .001$; 60% vs. 10% in the ITT analysis), with concordant secondary gains in VAS (62% vs. 8.5% reduction), BPIF, PGIC, and MPQ-SF-2; no serious adverse events occurred. Study characteristics and results are summarized in Tables 19 and 20. Study limitations are summarized in Tables 21 and 22.

Table 19. Summary of Key Randomized Controlled Trials Characteristics

Trial	Countries	Sites	Dates	Participant	Interventions	
					Active	Comparator
Hayek et al (2025); CFPNS	US	7	2017-2021	Refractory chronic craniofacial neuropathic pain in trigeminal & occipital nerve distributions	HF electromagnetic-coupling permanent PNS, Freedom (Curonix), K233162; all implanted, 7-day responder run-in, then continued stimulation (n=28; mITT 26)	Device deactivation (transmitter off) for 3 mo, then reactivated (n=28; mITT 26)

mITT: modified intention-to-treat; PNS: peripheral nerve stimulation; US: United States.

Table 20. Summary of Key Randomized Controlled Trials Results

Study	$\geq 50\%$ Pain Relief (%)	VAS Pain Reduction (%)	Change in BPIF	Change in PGIC	Change in SF-36 MCS	Change in MPQ-SF-2
Hayek et al (2025); CFPNS	N	N	N	N	N	
Active (n=26)	69	62	3.6	4.9	-6.1	2.7
Deactivated (n=26)	11	8.5	0.1	1.7	2.0	-0.9
p-value	<.001	<.001	<.001	<.001	.01	<.001

BPIF: Brief Pain Inventory–Facial; MCS: mental component summary; MPQ-SF-2: Short-Form McGill Pain Questionnaire-2; PGIC: patient global impression of change; SF-36: 36-Item Short Form Health Survey; VAS: visual analog scale.

Table 21. Study of Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-up ^e
Hayek et al (2025); CFPNS		5. Direct-to-permanent implant with enriched 7-day responder run-in (no separate trial phase).	5. Comparator is device deactivation among an enriched responder pool, not a naive sham.		1. Concurrent-controlled comparison limited to 3 months (deactivated arm reactivated thereafter).

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^aPopulation key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

^bIntervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5. Other.

^cComparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

^dOutcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

^eFollow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 22. Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical ^f
Hayek et al (2025); CFPNS	4. Baseline VAS imbalance between arms (78.4 vs 68.3; $p=.01$); analyzed as change from baseline.	1. Unblinded; control is external transmitter on/off, so participants and assessors are not blinded.			4. Small randomized sample (52 mITT) after 93% run-in enrichment.	5. SF-36 PCS reported favorably ($p=.02$) without meeting the pre-specified Bonferroni threshold (.0167).

mITT: modified intention-to-treat; PCS: physical component summary; SF-36: 36-Item Short Form Health Survey; VAS: visual analog scale.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^aAllocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.

^bBlinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.

^cSelective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.

^dData Completeness key: 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); 7. Other.

^ePower key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.

^fStatistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Section Summary: Craniofacial Pain

The evidence for permanent PNS in individuals with refractory chronic craniofacial neuropathic pain includes a single multicenter RCT conducted under an FDA investigational device exemption (Hayek et al [2025], the CFPNS trial; N=60) using an enriched-enrollment, randomized-withdrawal design in which all participants were permanently implanted, responders during a 7-day assessment (56/60; 93%) were

randomized to continued stimulation or 3-month device deactivation. Relevant outcomes are symptoms, medication use, and quality of life. At the 3-month primary endpoint, 69% of the active arm versus 11% of the deactivated arm achieved $\geq 50\%$ pain relief (60% vs. 10% in the intention-to-treat analysis), with concordant secondary improvements in VAS, BPIF, PGIC, and MPQ-SF-2 and no serious adverse events. Limitations include the single-trial evidence base, the enriched-enrollment design (which restricts randomization to early responders and may overstate the effect relative to an all-comers population), and the short (3-month) blinded withdrawal window. Additional evidence from independent RCTs with all-comers enrollment and longer comparative follow-up is needed to determine the effect of permanent PNS on the net health outcome in this population.

Restorative Neurostimulation Therapy

Clinical Context and Therapy Purpose

The purpose of restorative neurostimulation therapy in individuals with chronic pain conditions is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with chronic musculoskeletal or neuropathic pain conditions, including chronic low back pain (CLBP).

Interventions

The therapy being considered is restorative neurostimulation therapy. The ReActiv8 System is an implantable electrical neurostimulation system that stimulates the nerves that innervate the lumbar multifidus muscles.

Comparators

The following practice is currently being used: continued medical management.

Outcomes

Specific outcomes of interest for individuals with chronic pain are listed in Table 24. The potential beneficial outcomes of primary interest would be improvements in pain, functioning, and quality of life.

Table 24. Outcome of Interest for Individual with Chronic Pain

Outcomes	Details
Morbid events	Opioid addiction, adverse events
Health status measures	Pain relief, functional status

Outcomes	Details
Medication use	Number of unsuccessful medication trials, amount of medications needed, dose of medication, dose frequency

The IMMPACT recommends that chronic pain trials should consider assessing outcomes representing 6 core domains: pain, physical functioning, emotional functioning, participant ratings of improvement and satisfaction with treatment, symptoms and adverse events, and participant disposition. Table 2 summarizes provisional benchmarks for interpreting changes in chronic pain clinical trial outcome measures per IMMPACT.

Regarding optimal timing of outcome assessment, this varies with pain setting. Per IMMPACT, recommended assessment timing includes at 3, 6, and 12 months in individuals with chronic low back pain.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Bess et al (2025) identified 6 prospective studies (N=650; 2 RCTs [see below]) evaluating restorative neurostimulation in patients with multifidus dysfunction and chronic low back pain. At 1 year, restorative neurostimulation reduced NRS by a mean of 3.2 points, Oswestry Disability Index (ODI) by 16.8 points, and an improvement in health-related quality of life (EQ-5D) of 0.200. At 4 years, there was a weighted average reduction in NRS pain of 4.1, a 22.7 point reduction in ODI, and an EQ-5D improvement of 0.251. The only trial with an active comparator was the RESTORE trial (see Schwab et al 2025 below) which had NRS reduction of 0.5, ODI improvement of 2.9, and EQ-5D improvement of 0.013 at 1 year.

Randomized Controlled Trial

Restorative neurostimulation therapy with the ReActiv8 system has been evaluated in a multicenter, sham-controlled RCT enrolling 204 individuals with chronic, refractory low back pain (ReActiv8-B, NCT02577354). Study characteristics are summarized in Table 25. Control group participants received treatment with the ReActiv8 system set to deliver low-level stimulation. The primary endpoint was the difference in proportions of responders in the treatment and control groups. Response was defined as the composite of 30% or greater reduction in VAS and no increase in pain medications, assessed at 120 days. Following the 120-day randomized phase, participants in the control group were given the option to

cross over to the intervention group and were followed along with the participants from the intervention group for up to 3 years. Primary study results were reported by Gilligan et al (2021). Information on the RCT is also included in the FDA Summary of Safety and Effectiveness Data conducted as part of the premarket approval process. At 120 days, there was no difference between groups on the primary endpoint of treatment response (57.1% intervention vs 46.6% sham; $p = .1377$) or the individual components of the primary endpoint (see Table 26). The study investigators conducted prespecified secondary analyses of the primary outcome data, including the between-group difference in VAS at 120 days, a review of participants with increased pain medications, and a cumulative-proportion-of-responders analysis, which graphically displays the proportion of responders across the range of all possible cutoffs and is described as having greater statistical power than the comparison of proportions of the dichotomized primary outcome. The VAS mean change from baseline to 120 days favored the intervention group (-3.3 vs -2.4; $p = .032$), but it is unclear if the difference between groups (0.9 points) was clinically meaningful. The cumulative proportion-of-responders analysis similarly favored the intervention group ($p = .0499$). Nine participants in both the intervention and control groups had an increase in pain medication at 120 days, but the increase was unrelated to low back pain in 6 of 9 participants in the treatment group versus 0 of 9 in the control group. Study limitations are summarized in Tables 27 and 28. Most importantly, the controlled phase was only 120 days. In the longer-term, uncontrolled follow-up phase of the trial, there was continued improvement in VAS scores over time in those who were assessed, but the lack of a control group and high attrition limits drawing conclusions from these results. Data was available for 176 of 204 participants at 1 year (86.3%), 156 of 204 participants (79%) at 2 years, 40, and 130 of 204 (63.7%) at 3 years. Gilligan et al (2024) reported follow-up at 5 years. A total of 126 patients were included and back pain VAS improved from 7.3 at baseline to 2.3 at 5-year follow-up with 71.8% of participants reporting a reduction of at least 50%. ODI scores and EQ-5D scores were also improved at long-term follow-up.

Schwab et al (2025) conducted a multicenter, open-label RCT investigating the effect of restorative neurostimulation therapy using the ReActiv8 system compared to optimal medical management (OMM) for treating chronic low back pain (CLBP) due to multifidus dysfunction (N=203) (RESTORE, NCT04803214). Participants were randomized to either restorative neurostimulation (n=99) or OMM (n=104). The primary endpoint was the mean change in the Oswestry Disability Index (ODI) at 1 year. Study characteristics and primary results are summarized in Tables 6 and 7. The results showed a significant improvement in ODI for the treatment arm compared to the control arm (ODI: 19.7 ± 1.4 vs. 2.9 ± 1.4 ; $p < .001$). Secondary endpoints also showed significant improvements in the numeric rating scale (NRS) in the treatment arm compared to the control arm for pain (3.6 ± 0.2 vs. 0.6 ± 0.2 ; $p < .001$) and health-related quality of life (EQ-5D-5L) (0.155 ± 0.012 vs. 0.008 ± 0.012 ; $p < .001$). 72% of patients in the treatment arm reached the composite endpoint of ≥ 15 -point ODI improvement and/or $\geq 50\%$ NRS improvement, compared to 11% in the control arm ($p < .001$). Safety outcomes indicated that 31 device-, procedure-, and/or therapy-related adverse events occurred in 23 (23.2%) patients in the treatment arm, with common events including implant site pocket pain (8.1%), device overstimulation (5.1%), and lead fracture (3.0%). Study limitations are summarized in Tables 8 and 9. Several limitations were identified. Participants were not blinded which could have led to placebo effects in the treatment arm and nocebo effects in the control arm. The treatment arm received more clinical contact than standard management protocols for restorative neurostimulation therapy which could artificially inflate healthcare utilization in the short term. There was a statistically significant imbalance in baseline depression with more active depression in the control arm than the treatment arm which could bias the effectiveness of treatment. Changes in medication were collected but not reported in the published analysis.

Smuck et al (2025) conducted a post-hoc reanalysis of the sham-controlled pivotal trial (ReActiv8-B, N=204) to evaluate categorical responder rates using common clinically relevant improvement thresholds that were not included in the original trial's analysis plan. Using a complete-case analysis (n=201 at 120

days), the reanalysis reported statistically significant differences favoring treatment over sham for ODI improvement at the ≥ 15 -point threshold (59.0% vs 40.6%; $p=.0111$) and $\geq 30\%$ threshold (65.0% vs 47.5%; $p=.0156$), EQ-5D improvement at the ≥ 0.15 -point threshold (57.0% vs 36.0%; $p=.0045$), and subject global impression of change of "better" or more (54.0% vs 33.7%; $p=.0045$). However, categorical pain responder rates on VAS did not differ significantly at the ≥ 2 -point threshold (61.0% vs 49.5%; $p=.1192$) or $\geq 50\%$ improvement threshold (45.0% vs 35.6%; $p=.1971$), although mean VAS change favored treatment (-3.3 vs -2.4 ; $p=.0209$). This study has limitations. As a post-hoc reanalysis, the outcome thresholds reported were not included in the original trial's prespecified statistical analysis plan, introducing the potential for selective reporting bias. The reanalysis used a complete-case analysis that modified the population handling of the original intention-to-treat analysis, including all participants without regard to the pain medication log criterion used in the original primary endpoint. Additionally, the 120-day follow-up may not capture the full treatment effect, and these results do not provide information regarding longer-term outcomes.

Table 25. Randomized Controlled Trial of Restorative Neurostimulation Therapy (ReActiv8) for Chronic Low Back Pain: Study Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Gilligan et al (2021) NCT02577354	US, Australia	26	2016-2018	N = 204 Age 22 to 75 years with nonneuropathic mechanical chronic LBP with pain on at least half of the days in the prior year, and continuing LBP despite 90 days of medical management; positive prone instability test suggesting impaired motor control of the multifidus muscle and consequent lumbar segmental instability	Restorative neurostimulation therapy with the ReActiv8 System programmed to a patient appropriate stimulation level	Active sham (ReActiv8 programmed to deliver low level stimulation)
Schwab et al (2025) NCT04803214	US	25	2021-2023	N=203 Ages 21 to 74 years with moderate to severe pain and disability associated with CLBP persisting for longer than 6 months (NRS: 6 to 9 and ODI: 30 to 60) and had failed previous treatments, including pain medications and physical therapy; all participants had evidence of lumbar multifidus muscle dysfunction, confirmed by physical assessment or MRI imaging	Restorative neurostimulation therapy with the ReActiv8 system	Optimal medical management treatment plan that was established prior to randomization

CLBP: chronic low back pain; LBP: low back pain; MRI, magnetic resonance imaging; NRS, numeric rating scale; ODI, Oswestry Disability Index.

Table 26. Randomized Controlled Trial of Restorative Neurostimulation Therapy (ReActiv8) for Chronic Low Back Pain: Results

Study	Primary Outcome: Response ($\geq 30\%$ reduction in VAS and no increase in pain medications at day 120)	VAS Response at day 120 (component of primary endpoint)	Increase in pain medication at 120-day visit (component of primary endpoint)	Mean Change in VAS at day 120 (SD)	Primary Outcome: Change in ODI at 1 year, mean $\pm$ SE
Gilligan et al (2021) NCT02577354	204	102	201	201	
ReActiv8	57.1%	58.8%	9 (6 unrelated to LBP)	-3.3 (2.7)	
Sham Control	46.6%	48.6%	9 (0 unrelated to LBP)	-2.4 (2.9)	
Difference (95% CI)	10.4% (-3.3% to 24.1%)			0.9	
p-value	.1377	.1438	NA	.032	
Schwab et al (2025) NCT04803214					203
ReActiv8 (n=99)					-19.7 $\pm$ 1.4
OMM (n=104)					-2.9 $\pm$ 1.4
Difference (95% CI)					-16.8 $\pm$ 1.9 (-20.6 to -13.0)
p-value					<.001

CI: confidence interval; LBP: low back pain; NA: not applicable; ODI, Oswestry Disability Index; OMM, optimal medical management; SD: standard deviation; SE, standard error; VAS: visual analog scale.

Table 27. Randomized Controlled Trial of Restorative Neurostimulation Therapy (ReActiv8) for Chronic Low Back Pain: Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-up ^e
Gilligan et al (2021) NCT02577354	4. Race/ethnicity of participants not reported				1. Follow-up was 120 days in controlled phase
Schwab et al (2025) NCT04803214	5. Statistically significant imbalance in baseline depression between treatment and control arms	5. Greater clinical contact than standard management protocols in the treatment arm			

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5. Other.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not

supported; 7. Other.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 28. Randomized Controlled Trial of Restorative Neurostimulation Therapy (ReActiv8) for Chronic Low Back Pain: Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical ^f
Gilligan et al (2021) NCT02577354				1. high attrition in longer-term, uncontrolled phase		
Schwab et al (2025) NCT04803214		1. Participants and study staff not blinded				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.

^b Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.

^d Data Completeness key: 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); 7. Other.

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Nonrandomized Studies

Nonrandomized studies of restorative neurostimulation therapy for chronic low back pain are at high risk of bias due to lack of blinding, small sample sizes, high attrition, and no sham control, but are briefly discussed here for completeness. A prospective single-arm trial (ReActiv8-A; NCT01985230) was conducted at 9 sites in the United Kingdom, Belgium, and Australia to assess technical feasibility, performance, and safety of the ReActiv8 system. Participants were followed at 45, 90, 180, and 270 days, then annually for 4 years. Results at 1 year (Deckers et al 2018), 2 years (Thomson et al 2021), and 4 years (Mitchell et al 2021) have been published. Of 53 participants enrolled, 33 completed 4-year follow-up. Of these, 73% had a clinically meaningful improvement of 2 points or greater on the low back pain Numeric Rating Scale and 76% had an improvement of 10 points or greater on the Oswestry Disability Scale (Mitchell et al 2021). A case series (N = 44) published in 2022 reported the experience of a single surgeon in Germany (Ardeshiri et al 2022). After 1 year of therapy, 68% of individuals with refractory chronic low back pain who received treatment with the ReActiv8 device had moderate (30% or greater) reductions in pain and 52% had substantial (greater than 50%) reductions in pain.

Section Summary: Restorative Neurostimulation Therapy

The evidence includes a systematic review, 1 sham-controlled RCT (N = 204), 1 open-label RCT (N=203), 1 prospective single-arm trial (N = 53), and a case series (N = 44). In the sham-controlled RCT, there was no difference between groups on the primary endpoint of treatment response at 120 days, defined as the composite of 30% or greater reduction in VAS and no increase in pain medications (57.1% intervention vs 46.6% sham; p = .1377). Prespecified secondary analyses of primary outcome data

avored the intervention group, but clinical significance is unclear. An uncontrolled follow-up phase of the RCT reported continued improvement in pain scores through 5 years but results are at high risk of bias due to lack of a control group and high attrition. The open-label RCT showed statistically significant improvements in the treatment arm compared to the control arm in the primary and secondary outcomes. However, limitations included lack of blinding, imbalance in baseline depression between treatment and control arms, and greater clinical contact than standard management protocols in the treatment arm. Nonrandomized studies are limited by lack of blinding, no sham control, high attrition, and small sample sizes. Additional evidence from longer-term sham controlled RCTs is needed.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

The American Society of Interventional Pain Physicians

In 2024, the American Society of Interventional Pain Physicians (ASIPP) published guidelines on the use of peripheral nerve stimulation systems (e.g., ReActiv8) for the treatments of moderate to severe chronic refractory pain. Table 29 includes relevant recommendations from these guidelines.

Table 29. ASIPP Peripheral Nerve Stimulation Guidelines

Recommendations	LOE	SOR
The evidence of effectiveness of peripheral nerve stimulation in managing chronic pain, based on evidence synthesis utilizing comprehensive and systematic review of the literature with methodologic quality assessment of all studies, applying GRADE criteria, and best evidence synthesis for implantable peripheral nerve stimulation systems following a trial or selective lumbar medial branch stimulation without a trial, is Level III or fair with moderate certainty utilizing GRADE criteria.	Fair	Moderate
The evidence of effectiveness of peripheral nerve stimulation in managing chronic pain based on evidence synthesis utilizing comprehensive and systematic review of the literature with methodologic quality assessment of all studies, applying GRADE criteria, and best evidence synthesis for implantable stimulation systems following temporary peripheral nerve stimulation for 60 days is Level III or fair with moderate certainty utilizing GRADE criteria.	Fair	Moderate
Based on the evidence and the recommendations, indications may be expanded from present CMS guidance with addition of craniofacial pain, phantom limb pain, and low back pain, either nociceptive or neuropathic, with present evidence showing Level III or fair with moderate certainty utilizing GRADE criteria.	Fair	Moderate

LOE: level of evidence; SOR: strength of recommendation

Implantable Peripheral Nerve Stimulation

In 2022, the American Society of Pain and Neuroscience issued an evidence based clinical guideline for interventional treatments for low back pain which included the following recommendation related to peripheral nerve stimulation:

Recommendations for Multifidus Activation via Medical Branch Nerve Stimulation

- “Percutaneous 60-day PNS may provide sustained improvements in pain and function (Grade C, Level of Certainty Moderate).”
- “Percutaneous PNS may reduce or eliminate need for analgesics in individuals with chronic LBP (Grade C, Level of Certainty Low).”

Table 30. Quality of Evidence Ranking using United States Preventative Services Task Force Criteria Modified for Interventional Spine Procedures

Grade	Definition	Suggestions for Practice
A	The ASPN Back Group recommends the service. There is a high certainty that the net benefit is substantial.	Offer or provide this service.
B	The ASPN Back Group recommends the service. There is a high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The ASPN Back Group recommends selectively offering or providing this service to individual patients based on professional judgement and patient preferences. There is a least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The ASPN Back Group recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I Statement	The ASPN Back Group concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

American Society of Pain and Neuroscience: 60-day Peripheral Nerve Stimulation (NEURON Living Guideline)

In 2025, the American Society of Pain and Neuroscience (ASPN) published a NEURON living-guideline addressing the use of 60-day peripheral nerve stimulation therapy. The guidance seeks to clarify the distinctions among trial stimulation, permanent implantation, and the fixed 60-day treatment approach, and offers best-practice consensus points derived from an evidence-graded assessment combined with expert clinical opinion. This was an expert consensus rather than a de novo systematic review.

American Society of Pain and Neuroscience: Peripheral Nerve Stimulation (NEURON Project)

In 2025, the ASPN published a NEURON consensus guideline on the use of peripheral nerve stimulation for chronic pain and neurological conditions, updating and expanding its prior review of the evidence and providing consensus best-practice recommendations across anatomic targets and indications. This document reflects evidence-graded expert consensus rather than a de novo systematic review.

Restorative Neurostimulation Therapy

In 2022, the American Society of Pain and Neuroscience (ASPN) published consensus clinical guidelines for the use of implantable peripheral nerve stimulation (e.g., ReActiv8) in the treatment of chronic pain based on a review of the literature through March 2021. Relevant recommendations for best practices pertinent to this review are listed below in Table 31.

Table 31. American Society of Pain and Neuroscience Best Practices Peripheral Nerve Stimulation Guidelines

Recommendations	LOE	DOR
<i>Upper Extremities</i>		
PNS may offer modest and short-term pain relief, improved physical function, and better quality of life for chronic hemiplegic shoulder pain.	I	B
PNS for mononeuropathies of the upper extremity may be offered following a positive diagnostic ultrasound-guided nerve block of the targeted nerve and is associated with modest to moderate pain relief.	II-2	B
<i>Lower Extremities</i>		
PNS may be considered for lower extremity neuropathic pain following failure of conservative treatment options and is associated with modest pain relief.	I	B
PNS may be considered for lower extremity post-amputation pain following failure of conservative treatment options and is associated with modest to moderate pain relief.	I	B

DOR: degree of recommendation; LOE: level of evidence; PNS: peripheral nerve stimulation.

National Institute for Health and Care Excellence

In September 2022, NICE published guidance on neurostimulation of lumbar muscles with the ReActiv8 system for refractory non-specific chronic low back pain.

The guidance was based on a rapid review conducted in July 2021 and included the following statements:

- "Evidence on the efficacy and safety of neurostimulation of lumbar muscles for refractory non-specific chronic low back pain is limited in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research."

- "Further research should include suitably powered randomised controlled trials comparing the procedure with current best practice with appropriate duration. It should report details of patient selection and long-term outcomes."

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review can be located at clinicaltrials.gov.

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CODES

To report provider services, use appropriate CPT codes, HCPCS codes, Revenue codes, and/or ICD diagnosis codes.

Codes	Number	Description
CPT		
	64555	Percutaneous implantation of neurostimulator electrode array; peripheral nerve
	64575	Open implantation of neurostimulator electrode array; peripheral nerve (excludes sacral nerve)
	64585	Revision or removal of peripheral neurostimulator electrode array

Codes	Number	Description
	64590	Insertion or replacement of peripheral, sacral, or gastric neurostimulator pulse generator or receiver, requiring pocket creation and connection between electrode array and pulse generator or receiver
	64595	Revision or removal of peripheral, sacral, or gastric neurostimulator pulse generator or receiver, with detachable connection to electrode array
	64596	Insertion or replacement of percutaneous electrode array, peripheral nerve, with integrated neurostimulator, including imaging guidance, when performed; initial electrode array
	64597	Insertion or replacement of percutaneous electrode array, peripheral nerve, with integrated neurostimulator, including imaging guidance, when performed; each additional electrode array (List separately in addition to code for primary procedure)
	64598	Revision or removal of neurostimulator electrode array, peripheral nerve, with integrated neurostimulator
	64999	Unlisted procedure, nervous system (May be utilized for ReActive8)
	95970	Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group(s), interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve, neurostimulator pulse generator/transmitter, without programming
	95971	Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group(s), interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with simple spinal cord or peripheral nerve (e.g., sacral nerve) neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional
	95972	Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group(s), interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with complex spinal cord or peripheral nerve (e.g., sacral nerve) neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional

Codes	Number	Description
HCPCS		
	C1767	Generator neurostimulator (implantable) non-rechargeable
	C1778	Lead, neurostimulator
	C1787	Patient programmer, neurostimulator
	C1816	Receiver and/or transmitter, neurostimulation (implantable)
	C1820	Generator, neurostimulator (implantable), with rechargeable battery and charging system
	C1822	Generator, neurostimulator (implantable), high frequency, with rechargeable battery and charging system
	C1883	Adaptor/extension, pacing lead or neurostimulator lead (implantable)
	C1897	Lead, neurostimulator test kit (implantable)
	C9807	Nerve stimulator, percutaneous, peripheral (e.g., sprint peripheral nerve stimulation system), including electrode and all disposable system components, non-opioid medical device (SPRINT PNS)
	L8679	Implantable neurostimulator, pulse generator, any type
	L8680	Implantable neurostimulator electrode, each
	L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only
	L8682	Implantable neurostimulator radiofrequency receiver
	L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
	L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
	L8686	Implantable neurostimulator pulse generator, single array, nonrechargeable, includes extension
	L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
	L8688	Implantable neurostimulator pulse generator, dual array, nonrechargeable, includes extension
	L8689	External recharging system for battery (internal) for use with implantable neurostimulator, replacement only

Codes	Number	Description
Type of Service	Surgical	
Place of Service	Inpatient/Outpatient	

POLICY HISTORY

Date	Reason	Action
August 2026	Annual Review	Policy Revised
August 2025	Annual Review	Policy Revised
July 2024	Annual Review	Policy Revised
October 2023	Annual Review	Policy Revised
October 2022	Annual Review	Policy Revised
October 2021	Annual Review	Policy Renewed
October 2020	Annual Review	Policy Renewed
October 2019	Annual Review	Policy Renewed
October 2018		New Policy Created

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
 Medical Policy Analyst
 PO Box 9232
 Des Moines, IA 50306-9232

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