Electrical Stimulation for the Treatment of Pain and Muscle Rehabilitation (for Indiana Only)

Policy Number: CS036IN.09
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Ü Instructions for Use

Table of Contents **Page**

Related Policies

- Durable Medical Equipment, Orthotics, Medical Supplies, and Repairs/Replacements (for Indiana Only)
- Occipital Nerve Injections and Ablation (Including Occipital Neuralgia and Headache) (for Indiana Only)

Application

This Medical Policy only applies to the state of Indiana.

Coverage Rationale

Transcutaneous electrical nerve stimulator (TENS) is proven and medically necessary in certain circumstances. For medical necessity clinical coverage criteria, refer to the InterQual® CP: Durable Medical Equipment, Transcutaneous Electrical Nerve Stimulation (TENS).

Click here to view the InterQual® criteria.

Transcutaneous Electrical Joint Stimulation is not considered medically necessary. For medical necessity clinical coverage criteria, refer to the InterQual® Medicare: Post Acute & Durable Medical Equipment, Transcutaneous Electrical Joint Stimulation Devices (TEJSD).

Click here to view the InterQual® criteria.

Neuromuscular Electrical Stimulation (NMES) and Functional Electrical Stimulation (FES) are medically necessary in certain circumstances. For medical necessity clinical coverage criteria, refer to the InterQual® Medicare: Post Acute & Durable Medical Equipment, Neuromuscular Electrical Stimulation (NMES) NCD.

Click here to view the InterQual® criteria.

The following are unproven and not medically necessary due to insufficient evidence of efficacy:

- Interferential therapy (IFT) for treating musculoskeletal disorders/injuries or to facilitate healing of nonsurgical soft tissue injuries or bone fractures
- Microcurrent electrical nerve stimulation (MENS)
- Percutaneous electrical nerve stimulation (PENS) or percutaneous neuromodulation therapy (PNT)
- Percutaneous electrical nerve field stimulation (PENFS)
- Percutaneous peripheral nerve stimulation (PNS)*
- Peripheral subcutaneous field stimulation (PSFS) or peripheral nerve field stimulation (PNFS)
- Pulsed electrical stimulation (PES)

- Restorative neurostimulation
- Scrambler therapy (ST)
- Translingual stimulation for gait rehabilitation (TS)

*For information regarding percutaneous peripheral nerve stimulation for occipital neuralgia and headache, refer to the Medical Policy titled Occipital Nerve Injections and Ablation (Including Occipital Neuralgia and Headache) (for Indiana Only).

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
*0278T	Transcutaneous electrical modulation pain reprocessing (e.g., scrambler therapy), each treatment session (includes placement of electrodes)
*0720T	Percutaneous electrical nerve field stimulation, cranial nerves, without implantation
*0783T	Transcutaneous auricular neurostimulation, set-up, calibration, and patient education on use of equipment
*63650	Percutaneous implantation of neurostimulator electrode array, epidural
*63655	Laminectomy for implantation of neurostimulator electrodes, plate/paddle, epidural
*63663	Revision including replacement, when performed, of spinal neurostimulator electrode percutaneous array(s), including fluoroscopy, when performed
*63664	Revision including replacement, when performed, of spinal neurostimulator electrode plate/paddle(s) placed via laminotomy or laminectomy, including fluoroscopy, when performed
*63685	Insertion or replacement of spinal neurostimulator pulse generator or receiver, requiring pocket creation and connection between electrode array and pulse generator or receiver
64555	Percutaneous implantation of neurostimulator electrode array; peripheral nerve (excludes sacral nerve)
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

**Note: The following are the only FES devices verified by the Centers for Medicare & Medicaid Services (CMS) Pricing, Data Analysis and Coding (PDAC) to be reported with HCPCS code E0770:

- NESS L300 and H200 devices (Bioness)
- Odstock ODFS Pace FES System (Odstock Medical/Boston Brace)
- WalkAide (Innovative Neurotronics)
- Deluxe Digital Electronic Muscle Stimulator (Drive Medical)

HCPCS Code	Description
*A4438	Adhesive clip applied to the skin to secure external electrical nerve stimulator controller, each
*A4556	Electrodes (e.g., apnea monitor), per pair
*A4557	Lead wires (e.g., apnea monitor), per pair
*A4593	Neuromodulation stimulator system, adjunct to rehabilitation therapy regime, controller

HCPCS Code	Description
*A4594	Neuromodulation stimulator system, adjunct to rehabilitation therapy regime, mouthpiece, each
*A4595	Electrical stimulator supplies, 2 lead, per month, (e.g., TENS, NMES)
*E0720	Transcutaneous electrical nerve stimulation (TENS) device, two-lead, localized stimulation
*E0730	Transcutaneous electrical nerve stimulation (TENS) device, four or more leads, for multiple nerve stimulation
*E0731	Form-fitting conductive garment for delivery of TENS or NMES (with conductive fibers separated from the patient's skin by layers of fabric)
*E0744	Neuromuscular stimulator for scoliosis
E0745	Neuromuscular stimulator, electronic shock unit
*E0762	Transcutaneous electrical joint stimulation device system, includes all accessories
*E0764	Functional neuromuscular stimulation, transcutaneous stimulation of sequential muscle groups of ambulation with computer control, used for walking by spinal cord injured, entire system, after completion of training program
E0770**	Functional electrical stimulator, transcutaneous stimulation of nerve and/or muscle groups, any type, complete system, not otherwise specified
*E1399	Durable medical equipment, miscellaneous
*L8678	Electrical stimulator supplies (external) for use with implantable neurostimulator, per month
L8679	Implantable neurostimulator, pulse generator, any type
L8680	Implantable neurostimulator electrode, each
L8682	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
*S8130	Interferential current stimulator, 2 channel
*S8131	Interferential current stimulator, 4 channel

Note: Codes labeled with an asterisk (*) are not managed for medical necessity review for the state of Indiana at the time this policy became effective. Refer to the most up to date prior authorization list for Indiana at Prior Authorization and Notification: UnitedHealthcare Community Plan of Indiana.

Coding Clarification: Transcutaneous electrical joint stimulation devices (HCPCS code E0762) are noninvasive devices that deliver low-amplitude pulsed electrical stimulation.

Description of Services

Electrical stimulators provide direct, alternating, pulsating and/or pulsed waveform forms of energy. The devices are used to exercise muscles, demonstrate a muscular response to stimulation of a nerve, relieve pain, relieve incontinence, and provide test measurements. Electrical stimulators may have controls for setting the pulse length, pulse repetition frequency, pulse amplitude, and triggering modes. Electrodes for such devices may be indwelling, implanted transcutaneous, or surface.

Functional Electrical Stimulation (FES)

FES is the direct application of electric current to intact nerve fibers in a coordinated fashion to cause involuntary but purposeful contraction. FES bypasses the central nervous system and targets motor neurons innervating either skeletal muscle or other organ systems. Electrodes may be on the surface of the skin or may be surgically implanted along with a stimulator. FES is categorized as therapeutic and functional. Therapeutic FES enables typically resistive exercise, with the goal of preventing muscular atrophy and promoting cardiovascular conditioning. Functional FES enables or enhances standing, ambulation, grasping, pinching, reaching, respiration, bowel or bladder voiding, or ejaculation. The two goals of FES are mutually supportive (Hayes, 2017).

Interferential Therapy (IFT)

IFT is a treatment modality that is proposed to relieve musculoskeletal pain and increase healing in soft tissue injuries and bone fractures. Two medium-frequency, pulsed currents are delivered via electrodes placed on the skin over the targeted area producing a low-frequency current. IFT delivers a crisscross current resulting in deeper muscle penetration. It is theorized that IFT prompts the body to secrete endorphins and other natural painkillers and stimulates parasympathetic nerve fibers to increase blood flow and reduce edema.

Microcurrent Electrical Nerve Stimulation Therapy (MENS)

MENS is intended for pain relief and to facilitate wound healing, delivering current in the microampere range. One micro amp (μA) equals 1/1000th of a milliamp (mA). By comparison, TENS therapy delivers currents in the milliamp range causing muscle contraction, pulsing, and tingling sensations. The microcurrent stimulus is sub sensorial, so users cannot not detect it. Although microcurrent devices are approved in the category of TENS for regulatory convenience, in practical use they are in no way similar and cannot be compared to TENS in their effect (Curtis, et al. 2010; Zuim, et al. 2006). MENS is also referred to as micro electrical therapy (MET) or micro electrical neuro-stimulation. Examples of MENS devices currently in use include, but are not limited to, Algonix®, Alpha-Stim®100, Electro-Myopulse 75L, electro-Lyoscope 85P, KFH Energy, MENS 2000-D, MICROCURRENT, Myopulse 75C, and Micro Plus™.

Neuromuscular Electrical Stimulation (NMES)

NMES involves the use of transcutaneous application of electrical currents to cause muscle contractions. The goal of NMES is to promote reinnervation, to prevent or retard disuse atrophy, to relax muscle spasms, and to promote voluntary control of muscles in individuals who have lost muscle function due to surgery, neurological injury, or disabling condition.

Percutaneous Electrical Nerve Stimulation (PENS)

PENS, also known as percutaneous neuromodulation therapy (PNT) , is a conservative, minimally invasive treatment for pain in which acupuncture-like needles connected through a cable to an external power source are inserted into the skin. Needle placement is near the area of pain and is percutaneous instead of cutaneous (e.g., TENS). PENS electrodes are not permanently implanted as in SCS. The mechanism of action of PENS is theorized to modulate the hypersensitivity of nerves from which the persistent pain arises, potentially involving endogenous opioid-like substances. Examples of PENS devices include, but are not limited to, and Neuro-Stim. While the term percutaneous neuromodulation therapy (PNT) is sometimes used interchangeably with PENS reports indicate PNT is a variant of PENS in which electrodes are placed in patterns that are uniquely different than placement in PENS (Hayes, 2019).

Percutaneous Electrical Nerve Field Stimulation (PENFS)

PENFS is a variation of PENS in that it uses a low-frequency electrical current to stimulate the skin and underlying tissues in a general area of pain rather than targeting a specific nerve. PENFS devices are thought to work by sending electrical stimulation of peripheral cranial neurovascular bundles in the external ear to help modulate central pain pathways; however, the exact mechanism responsible for the analgesic effects remains unknown.

Percutaneous Peripheral Nerve Stimulation (PNS)

PNS is a type of neuromodulation therapy where an electrode(s) is implanted near a peripheral nerve (i.e., nerve located outside of the brain and spinal cord) that subserves the painful dermatome. The electrode(s) deliver electrical impulses to the affected nerve to disrupt the transmission of pain signals thereby reducing the level of pain (International Neuromodulation Society, 2019). Implanted peripheral nerve stimulators include systems such as the ReActiv8 Implantable Neurostimulation System, StimRouter Neuromodulation System, SPRINT PNS System, and StimQ Peripheral Nerve Stimulator System.

Peripheral Subcutaneous Field Stimulation (PSFS)

PSFS, also known as peripheral nerve field stimulation (PNFS), is a technique used when the field to be stimulated is not well defined or does not fit exactly within the area served by any one or two peripheral nerves. Different from spinal cord stimulation (SCS) or peripheral nerve stimulation (PNS), the electrode arrays are implanted within the subcutaneous tissue of the painful area, not on or around identified neural structures, but most probably in or around cutaneous nerve endings of the intended nerve to stimulate (Abejon and Krames, 2009).

Pulsed Electrical Stimulation (PES)

PES is hypothesized to facilitate bone formation, cartilage repair, and alter inflammatory cell function. Some chondrocyte and osteoblast functions are mediated by electrical fields induced in the extracellular matrix by mechanical stresses.

Electrostatic and electrodynamic fields may also alter cyclic adenosine monophosphate or DNA synthesis in cartilage and bone cells.

Restorative Neurostimulation

Restorative neurostimulation is a minimally invasive method of innervating the multifidus muscle of the lower back to override the underlying cycle of lumbar multifidus muscle degeneration. It is intended to be used as a rehabilitative therapy for patients with impaired neuromuscular control associated with mechanical chronic low back pain (CLBP). After the neurostimulation device is implanted, isolated electrical impulses are stimulated by way of self-anchoring leads placed next to the medial branch of the dorsal ramus (Hayes, 2022).

Scrambler Therapy

Scrambler therapy (ST) [also referred to as Calmare Pain Therapy (Calmare Therapeutics Inc.) or transcutaneous electronic modulation pain reprocessing], is a noninvasive, transdermal treatment designed for the symptomatic relief of chronic pain. Treatment is performed by applying electrodes corresponding to the dermatome on the skin just above and below the area of pain. The device provides electrical signals via the electrodes presenting non-pain information to the painful area using continuously changing, variable, nonlinear waveforms (Hayes, 2021).

Transcutaneous Electrical Nerve Stimulation (TENS)

A TENS is a device that utilizes electrical current delivered through electrodes placed on the surface of the skin to decrease the perception of pain by inhibiting the transmission of afferent pain nerve impulses and/or stimulating the release of endorphins. A TENS unit must be distinguished from other electrical stimulators (e.g., neuromuscular stimulators) which are used to directly stimulate muscles and/or motor nerves.

Translingual Stimulation

Translingual stimulation (TLS) is a noninvasive method used to elicit neural changes by stimulating the trigeminal and facial cranial nerves. Input from neurostimulation and physical therapy are thought to enhance neuroplasticity and enable the brain to restructure and relearn motor skills (ECRI, 2021).

Clinical Evidence

Interferential Therapy (IFT)

Low Back Pain

Espejo-Antúnez et al. (2021) conducted a randomized, single-blind, controlled trial to evaluate the effects caused by interferential current therapy (ICT) on perceived pain and heart rate variability (HRV) in patients with non-specific chronic low back pain (NSCLBP). In the study, a total of 49 patients with NSCLBP were randomly divided into an experimental (n = 25) and a sham group (n = 24). All participants received a single intervention, ICT, or simulated intervention during November 1, 2020, through November 30, 2020. Outcome measures including baseline (sit-down position) and postintervention (prone position) pain, heart rate (HR), time domain parameter (rMSSD), diameters of the Poincaré plot (SD1, SD2), stress score (SS), and sympathetic/parasympathetic (S/PS) ratio were investigated. In both groups, significant statistical differences were found in perceived pain and in all HRV parameters except in HRmax. Between-group comparisons showed differences in all variables except for HRmin and HRmean in favor of the experimental group. These changes reported an increase in parasympathetic activity (rMSSD) ($p < 0.05$) and a decrease in sympathetic activity (increase in SD2 and decrease in SS) ($p < 0.001$) and perceived pain ($p < 0.001$), with a greater size effect ($\eta 2 = 0.44$) in favor of the experimental group. The authors concluded that a single session of ICT can shift the autonomic balance towards increased parasympathetic dominance and decreased the sympathetic dominance and intensity of pain perceived by patients with NSCLBP. The primary limitation to this study was that ICT was carried out in a single session and exclusively to males. Also, the lack of measurement of psychosocial factors associated with persistent pain, which could influence HRV. Well designed, comparative studies with larger patient populations are needed to further describe safety and clinical outcomes.

Rajfur et al. (2017) conducted a pilot study to compare the effects of treating low back pain (LBP) using selected electrotherapy methods, assessing the influence of individual electrotherapeutic treatments on reduction of pain, improvement of the range of movement in lower section of the spine, and improvement of motor functions and mobility. Participants were assigned to 6 comparison groups: A - conventional TENS, B - acupuncture-like TENS, C - high-voltage ES, D - IFT stimulation, E - diadynamic current, and F - control group. Of the 127 qualified participants, 123 completed the 3-week study. Authors determined that selected electrical therapies (IFT, TENS < and high voltage ES) appear to be effective in treating chronic LBP.

Franco et al. (2016) conducted a double-blind single institution RCT on 148 patients with chronic nonspecific low back pain (LBP) to determine whether IFT before Pilates exercises is more effective than placebo. The primary outcome measures were pain intensity, pressure pain threshold, and disability after 6 weeks of therapy. The study groups consisted of active IFT + Pilates group, and placebo IFT + Pilates group. Eighteen treatment sessions were offered 3 times a week for 6 weeks. Both groups showed significant improvement in outcomes after 6 weeks, with improvements in pain and disability being considered clinically significant as well. However, the authors concluded that active IFT combined with Pilates exercises is no better than placebo IFC plus Pilates. Further studies are suggested.

To assess the influence of TENS and IFT on pain relief and to compare the analgesic efficacy of the 2 modalities, Grabiańska et al. (2015) studied 60 patients with LBP. The participants were equally and randomly divided into 2 groups. Depending on the groups, patients were given a series of ten 20-minute sessions over a 2-week period using either IFT or TENS currents. In all patients, VAS and Laitinen modified scale were taken before and after treatment. At the end of the 2 weeks, there was improvement in nearly all components of the VAS and Laitinen scale for both groups. There was no statistically significant difference between the groups in reducing the intensity and other aspects of pain (e.g., frequency, pain medication and activity limitation). The authors concluded that both IFT and TENS therapy are effective for pain relief in patients with LBP, as their study results demonstrated equal analgesic efficacy of both therapy modalities.

Hurley et al. (2004) investigated the outcomes of manipulative therapy and IFT used as sole modalities or in combination for treatment of acute LBP. Eighty patients received manipulative therapy, 80 received IFT, and 80 received a combination of both. The primary outcome was a change in functional disability on the Roland Morris Disability Questionnaire. Follow-up questionnaires were posted at discharge and at 6 and 12 months. At discharge, all interventions significantly reduced functional disability. At 12 months, there were no significant differences found between the groups for recurrence of back pain, work absenteeism, medication consumption, exercise participation or the use of healthcare. The authors concluded that there was no difference between the effects of a combined manipulative therapy and IFT package and either of the therapy modalities alone.

Osteoarthritis of the Knee/Anterior Cruciate Ligament/Meniscectomy/Knee Chondroplasty/Knee Arthroplasty

In a single-center, double-blind, placebo-controlled RCT to determine whether TENS and interferential current (IFC) treatments have any effect on central sensitization (CS) in patients with knee osteoarthritis (OA), Artuç et al.(2023) recruited 80 patients between 40 and 70 years of age. The participants were randomly assigned to one of the four treatment groups with 20 in each of the following groups: TENS, placebo-TENS, IFC, and placebo-IFC. All interventions were administered 5 times a week for 2 weeks. The primary outcome was pressure pain threshold (PPT) at the painful knee and at the shoulder as a painless distant point. Secondary outcome measures included the visual analog scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index, Timed Up and Go Test, pain catastrophizing scale, Beck Depression Inventory, and Tampa Scale of Kinesiophobia. The authors reported that all assessment parameters were improved without a significant difference among all four groups with the exception of PPT, which was significantly improved in the TENS and IVC groups when compared with the sham groups at 2 weeks and 3 months. The authors concluded that TENS and IFC reduced pain sensitivity as compared to the placebo groups in patients with knee OA and that this improvement was even more pronounced in the TENS group.

Chen et al. (2022a) conducted a systematic review and meta-analysis to assess the effectiveness of interferential current therapy (IFC) in patients with knee osteoarthritis. The authors searched PubMed, Cochrane Library, Embase, ClinicalKey, and Scopus for relevant studies from their date of launch to March 22, 2022. They included randomized controlled trials (RCTs) in which IFC was applied to knee osteoarthritis patients and the outcomes of pain scores or functional scales were assessed. Ten RCTs with 493 patients met the inclusion criteria. Nine RCTs were included in the meta-analysis. The IFC groups exhibited significant improvements relative to the control groups for short-term pain scores (SMD = -0.64, 95% CI -1.04 to -0.25, p = 0.001), long-term pain scores (SMD = -0.36, 95% CI - 0.60 to - 0.11, p = 0.005), and short-term Western Ontario and McMaster Universities Osteoarthritis Index scores (SMD = -0.39, 95% CI -0.77 to - 0.02, p = 0.04). All included studies did not observe any obvious adverse effects of IFC. The authors concluded that IFC can be recommended as a treatment for knee osteoarthritis because it improves short- and long-term pain and short-term function. However, they recommended large-scale and high-quality RCTs with longer follow-up to establish an appropriate standardized treatment. Limitations to this study include a moderate-to-high heterogeneity for some results as the IFC devices, IFC parameter settings, and treatment protocols used by the included studies were inconsistent. In addition, some of the included studies did not implement blinding of therapists and participants, resulting in risks of bias that may have affected the results of this study. Finally, five of the included 10 RCTs reported immediate outcome measurements upon treatment completion, thereby limiting the applicability of long-term results. Well designed, adequately powered, prospective, controlled clinical trials of IFC are needed to further describe safety and clinical efficacy. Authors Alqualo-Costa et al. (2021), which were previously cited in this policy, are included in this systematic and meta-analysis review.

Kadı et al (2019) conducted a single-center, double-blind RCT to investigate the effectiveness of IFT following total knee arthroplasty (TKA). Of the 98 people who completed the study, 49 were in the treatment group where they received IFT for 30 minutes, twice a day for five days post-operatively and 49 were in the sham control group where the same pads were applied but no IFT stimulation was given. At the baseline, there were no statistically significant differences between the groups in respect of demographic and clinical data. The authors concluded that no significant difference was seen between the two groups in respect of pain, range of motion and edema at days 0, 5, and 30 and that IFT did not show to be an effective modality for pain management in patients who had undergone TKA. They observed that the amount of paracetamol used was significantly lower in the IFT group; however, the authors noted that the difference did not continue after the end of the first month and they stated that this cannot be argued as showing the effectiveness of IFT. The main limitations documented by the authors included the relatively short duration of the treatment and the lack of preoperative data for the participants. They recommended high-quality, multi-center RCTs and studies with long-term follow-up be conducted to show the exact effects of ICT on functional recovery when it is added as a supplement to a postoperative rehabilitation program.

Zeng et al. (2015) performed a systematic review and Bayesian network meta-analysis of 27 RCTs over a 30-year period, which compared different ES therapies (high-frequency TENS (h-TENS), low-frequency TENS (l-TENS), NMES, IFC, PES and noninvasive interactive neurostimulation (NIN)) with the control group (sham or no intervention) for relief of knee pain in 1253 patients with OA. The primary goal was to identify whether or not the different ES modalities offered pain management by measuring the degree of pain intensity and the change pain score at last follow-up time point. Of the 6 therapy modalities, IFT was the only significantly effective treatment in both pain intensity and changed pain score at last follow-up time point when compared with the control group. In addition, IFT was deemed the best probable option for pain relief among the 6 therapy modalities. The authors' conclusions were that IFT was the most promising for management of knee pain related to OA. The other ES therapies were considered safe for patients with knee OA, although some were considered inappropriate. Study limitations included a small number of included trials, heterogeneity of the evidence, and the indirectness of comparisons inherent to network meta-analyses.

A multi-center, single-blind, RCT by Burch et al. (2008) investigated the benefits of combined interferential (IF) and patterned muscle stimulation in the treatment of OA of the knee. The study randomized 116 patients to a test or control group. The test group received 15 minutes of IF stimulation followed by 20 minutes of patterned muscle stimulation. The control group received 35 minutes of low-current TENS. Both groups were treated for 8 weeks. Subjects completed questionnaires at baseline and after 2, 4 and 8 weeks. Primary outcomes included the pain and physical function subscales of the WOMAC OA Index and VAS for pain and QOL. Compared to the control group, the test group showed reduced pain and increased function. The test group showed a greater decrease in the WOMAC pain subscale ($p = 0.002$), function subscale ($p = 0.003$) and stiffness subscale ($p = 0.004$). More than 70% of the test group, compared to less than 50% of the control group, had at least a 20% reduction in the WOMAC pain subscale. When analyzing only patients who completed the study (n = 49 in test group, n = 50 in control group), the test group had a nominally significant greater decrease in overall pain VAS. No significant differences were observed between groups related to incidence of adverse events (AEs). The authors concluded that in patients with OA of the knee, home-based patterned stimulation appears to be a promising therapy for relieving pain, decreasing stiffness, and increasing function. Study limitations included manufacturer sponsoring, 10% drop out rate and the treatment effect did not reflect a sufficient significant difference.

Other Musculoskeletal Pain

Katirci Kirmaci et al. (2023) conducted a single-blinded RCT to compare the effectiveness of TENS and interferential current (IFC) on pain, functional capacity, and quality of life (QOL) in patients with Multiple Sclerosis (pwMS). The study analyzed the results of 30 adult pwMS who were randomized into two groups with one group receiving TENS (n = 15) and the second group receiving IFC (n = 15). Each group received electrical stimulation therapy every day, 5 days a week for 4 weeks. A blinded physical therapist who did not know the treatment groups assignments made all evaluations, which were done before and after the treatment, while another physical therapist applied the treatments. The authors used the Visual Analogue Scale (VAS) to assess pain severity, the LANSS questionnaire to assess neuropathic pain, the 2-minute walk test (2MWT) was used to measure functional capacity and quality of life was evaluated with the 'Multiple Sclerosis International Quality of Life Scale (MusiQol). The authors reported that the most severe and mean VAS and LANSS results decreased significantly while the 2MWT and all of the sub-headings of the MusiQol, except for the relationship with the health system in the TENS group, increased significantly. The authors concluded that IFC and TENS decreased pain and increased functional capacity; however, the TENS application was more effective in increasing QOL.

In a systematic review and meta-analysis evaluating the efficacy of IFC in alleviating musculoskeletal pain in adults, Hussein et al (2021) reviewed 35 RCTs of variable methodological quality from which 19 trials were included in the meta-analysis. The RCTs included 14 studies involving low back pain (LBP), seven with shoulder issues, six with knee pain, five with neck pain, two with lumbar discogenic pain and one each for carpal tunnel syndrome and plantar fasciitis. In

reviewing the methodologies, the studies included six that were placebo-controlled, four that included IFC as part of the control or standard therapy and the remaining 25 included IFC as part of the experimental arm or compared IFC to another experimental treatment. The results of the critical appraisal for the studies revealed that 16 of the 35 RCTs were of high methodological quality, 16 were of medium quality, and three studies demonstrated low quality. The 19 trials that they included in the meta-analysis included a total sample size of 1,167 participants. The other trials were not included in the meta-analysis due to a lack of required data, the inclusion of IFC as part of the standard treatment arm or because they consisted of more than one experimental IFC or control group. The authors determined that, in general, IFC could have a significant pain-relieving effect compared to placebo; however, the low number of studies raised suspicions about this conclusion. The authors also concluded that IFC showed no significant difference when it was added to a standard treatment protocol compared to placebo plus standard treatment or compared to standard treatment alone. They also found that IFC showed no significant difference when compared to other single interventions such as laser, TENS, or cryotherapy. Limitations identified by the authors included the heterogeneity of the population of the trials, the exclusion of non-English language publications, the subjective nature of the pain measures and the lack of a validation study in the quality assessment method used in the review.

Albornoz-Cabello et al. (2019) conducted a single-blinded, single-center RCT to investigate the effects of adding IFT to usual care after surgery in adults with subacromial pain syndrome (SAPS). The study included 56 adults with SAPS who underwent acromioplasty in the past 12 weeks. All participants underwent a two-week intervention, three times a week of either a 15-minute IFT electro-massage plus usual care (treatment group; n = 28) or usual care only (control group; n = 28). There were no adverse reactions or dropouts during the study protocol . A blinded evaluator collected outcomes at baseline and after the last treatment session. The authors concluded that IFT plus usual care resulted in significant improvement in shoulder pain intensity, upper limb function, and shoulder flexion, abduction, internal and external rotation; however, there was no difference between groups for shoulder extension and adduction. The authors stated that the study was limited by the lack of a sham IFT group, that there was a lack of data beyond the immediate results after the last treatment and that the therapist that provided the interventions was not blinded to the participant allocation group. They recommend further research to investigate if different results would be expected using different IFT current parameters and to identify the medium and long-term effects of IFT on post-operative pain in adults with SAPS.

Dissanayake et al. (2016) compared the effectiveness of TENS and IFT in a single-blind RCT on individuals with myofascial pain syndrome (MPS). The aim of this study was to compare the effectiveness of these treatment modalities both in combination with hot pack, myofascial release, AROM exercise, and a home exercise program on MPS patients with upper trapezius myofascial trigger point. A total of 105 patients with an upper trapezius myofascial trigger point were randomly allocated to 3 groups, 3 therapeutic regimens-control-standard care (hot pack, AROM exercises, myofascial release, and a home exercise program with postural advice), TENS-standard care and IFT-standard care-were administered 8 times during 4 weeks at regular intervals. Pain intensity and cervical range of motions (cervical extension, lateral flexion to the contralateral side, and rotation to the ipsilateral side) were measured at baseline, immediately after the first treatment, before the eighth treatment, and 1 week after the eighth treatment. Immediate and short-term improvements were marked in the TENS group (n = 35) compared with the IFT group (n = 35) and the control group (n = 35) with respect to pain intensity and cervical range of motions. The IFT group showed more significant improvement on these outcome measurements than the control group did. The authors concluded that TENS with standard care facilitates recovery better than IFT does in the same combination.

To evaluate the effectiveness of passive physical modalities (which included IFT) on soft tissue injuries of the shoulder, Yu et al. (2015) conducted a systematic review of literature published between January 1, 1990, and April 18, 2013. RCTs and cohort and case-control studies were eligible. Of the 22 eligible articles, 11 studies were found to have a low risk of bias and so were analyzed, although the collective number of patients within the 11 studies was not cited. IFT was one of multiple modalities that were ineffective in reducing shoulder pain. The authors concluded that most passive physical modalities, including IFT, do not benefit patients with subacromial impingement syndrome.

Tibial Fractures

Fourie and Bower bank (1997) studied IFT as a treatment to accelerate healing of tibial fractures in a double blind, RCT. Forty-one men received IFT, 35 received sham, and 151 received no intervention. Outcomes were measured by the time to union or incidence of nonunion. IFTs were applied to the experimental group via suction electrodes for 30 minutes per day for 10 days. The placebo group had only suction electrodes applied producing a rhythmical massage effect. The control group received no intervention. The data analysis reflected no difference in the time for union in the 3 groups. The authors concluded that IFT did not reduce healing time for new tibial fractures or prevent nonunion, and that further investigation was recommended.

Clinical Practice Guidelines

National Institute for Health and Care Excellence (NICE)

NICE published a guideline for the management of knee osteoarthritis (OA) in which they concluded that IFT should not be offered to people with OA because there is insufficient evidence of benefit. The guideline stated that, although there were many studies on electrotherapy, the findings were inconsistent and mostly showed little benefit. The committee found that most studies were small with less than 100 participants and that the evidence from direct comparisons of electrotherapy with other interventions was uncertain (2022).

NICE guidance on the assessment and management of all chronic primary pain included guidance on TENS, ultrasound and IFT for chronic primary pain found no evidence for IFT. In the guidance, the committee stated that they found no evidence for IFT but they noted that IFT has been around for some time so that it is unlikely that new research will be done. The committee agreed that IFT should not be offered for chronic primary pain and made a recommendation against its use (2021).

NICE updated their guidance on the use of TENS, percutaneous electrical nerve simulation (PENS) and IFT for managing low back pain with or without sciatica and stated that these modalities should not be offered for treatment of low back pain with or without sciatica due to the paucity of evidence available that included mostly small individual studies of low or very low quality. No difference between interventions was seen when comparing IFT with sham or traction in people with low back pain without sciatica or when IFT was combined with education, exercise, and self-management. The committee found that the studies had inconsistencies across domains and in terms of their efficacy in long or short term. The Guideline Development Group concluded that there was a lack of evidence of clinical benefit to support a recommendation for the use of IFT as a treatment for low back pain or sciatica (2016, updated 2020).

American College of Physicians (ACP)

In their clinical practice guideline addressing noninvasive treatments for acute, subacute, and chronic LBP, the ACP states clinicians and patients should initially select non-pharmacologic treatments including but not limited to exercise (e.g., tai chi, yoga, motor control exercise) and multidisciplinary rehabilitation (e.g., ES therapies) when managing chronic LBP (Qaseem et al., 2017).

Pulsed Electrical Stimulation (PES)/Pulsed Electromagnetic Field (PEMF) Stimulation

Evidence on PES/PEMF is insufficient to support its use for the treatment of pain. More robust prospective controlled trials comparing PES or PEMF with placebo or alternative treatment modalities are needed to evaluate the efficacy of this treatment for chronic pain.

In their systematic review of systematic reviews (SR), Markovic et al. (2022) sought to provide an overview of application modalities and of the effectiveness of PEMF therapy in patients with osteoarthritis (OA), to summarize the current state of knowledge and to provide guidance to improve the quality of future studies. Their analysis consisted of 10 studies (including the Yang, 2020 and the Chen, 2019 SRs summarized below) with a total of 6,274 adult participants. All 10 of the included SRs focused on knee OA, while four also reported on cervical OA, two on hand OA and one on ankle OA. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used in all 10 studies as a measurement for physical function or disability and the visual analog scale was used in all 10 studies to assess pain. The authors reported that most studies were of low or medium quality. According to the authors, five of the 10 studies reported positive outcomes associated with the application of PEMF in patients with OA in terms of outcomes on disability or physical function and that five of the studies reported that PEMF had significant effects on pain reduction in patients with OA. Most consensus was observed by the authors for pain reduction, with other endpoints such as stiffness or physical function showing greater variability in outcomes. The authors noted that treatment protocols were very heterogeneous with the various levels of intensity, duration, and frequency of PEMF therapy utilized in the studies. The authors concluded that PEMF therapy appears to be effective in the short term to relieve pain and improve function in patients with OA even though the existing studies used very heterogeneous treatment regimens, had low sample sizes and suboptimal study designs.

Granja-Dominguez et al. (2022) conducted a single-center, randomized, placebo-controlled trial to investigate the effect of low-frequency pulsed electromagnetic field (PEMF) therapy on the level of fatigue, walking performance, symptoms of depression and quality of life (QOL) in patients with relapsing-remitting multiple sclerosis (RRMS). The study included 44 adults (84.4% female, mean age of 41 + 9.9 years) with RRMS who were randomly assigned to either the treatment group (n = 22) or the placebo group (n = 22) using a computer-generated random number sequence with the participants, outcome assessors and therapist blinded as to which study arm the participants were assigned. Each participant underwent a 4-week treatment protocol, 5 sessions per week for 45 minutes. The primary outcome was fatigue, which was assessed with the Fatigue Severity Scale (FSS) and the Modified Fatigue Impact Scale (MFIS). Secondary outcomes

included walking function (evaluated using the GAITRite system and the Timed 25-Foot Walk Test), the Beck Depression Inventory-II, and the Multiple Sclerosis International Quality of Life Questionnaire. Data were collected at baseline, after the 4-week protocol period, and at 3-months post-intervention. The authors reported that there were no changes from baseline for both fatigue measures between the PEMF treatment group and the placebo group at the end of treatment, nor were there any differences between groups for any of the secondary outcomes at post-intervention or at the 3-month follow up. The authors concluded that low-frequency PEMF therapy is no more effective than placebo to produce changes in fatigue, walking performance, severity of depression and QOL in people with RRMS.

D'Ambrosi et al. (2022) conducted a prospective randomized controlled trial (RCT) to assess pain relief and clinical outcomes in patients undergoing uni-compartmental knee arthroplasty (UKA) stimulated with pulsed electromagnetic fields (PEMFs) compared to a control group. A total of 72 patients undergoing medial UKA were randomized into a control group (n = 36) or an experimental PEMFs group (n = 36). The patients allocated to the experimental group were instructed to use PEMFs for 4 hours per day for 60 days. They were evaluated before surgery and then during the time points corresponding to 1 month, 2 months, 6 months, 12 months, and 36 months after the surgery. No placebo group was included in the RCT. Clinical assessment included the Visual Analogue Scale (VAS) for pain, Oxford Knee Score (OKS), the Short Form 36 (SF-36) health survey questionnaire, and joint swelling. During each follow-up visit, the consumption of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) was recorded. The VAS decreased on follow-up visits in both the groups; a statistical difference between the groups was observed during the 6 ($p = 0.0297$), 12 ($p = 0.0003$), and 36 months ($p = 0.0333$) follow-ups in favor of the PEMFs group. One month after UKA, the percentages of patients using NSAIDs in the PEMFs and control group were 71% and 92%, respectively ($p = 0.0320$). At the 2 months point, 15% of the patients in the PEMFs group used NSAIDs compared to 39% in the control group ($p = 0.0317$). The objective knee girth evaluation showed a statistically significant difference at 6 ($p = 0.0204$), 12 ($p = 0.0005$), and 36 ($p = 0.0005$) months with improved values observed in the PEMFs group. The subjective assessment of the swelling demonstrated a statistically significant difference at 2 ($p = 0.0073$), 6 ($p = 0.0006$), 12 ($p = 0.0001$), and 36 ($p = 0.0011$) months with better values noted in the PEMFs group. Last, the OKS result was higher in the experimental group during all the follow-ups (1mth: $p = 0.0295$; 2mths: $p = 0.0012$; 6mths: $p = 0.0001$; 12mths: $p < 0.0001$; 36mths: $p = 0.0061$). The authors concluded that the use of PEMFs leads to pain relief, clinical improvement, and lower NSAIDs consumption after medial UKA when compared to the control group. Limitations to this study include a lack of placebo group, small sample size, and use of a modified Cincinnati Rating System Questionnaire to assess patient satisfaction. Further research with additional randomized controlled trials is needed.

Pareja et al. (2022) conducted a randomized controlled trial (RCT) to investigate the therapeutic effects of pulsed electromagnetic field therapy (PEMF) via transcranial low-intensity magnetic stimulation (LIMS) in women diagnosed with fibromyalgia (FM) at 2, 12 and 24 weeks from the last LIMS administration treatment session. This study consisted of 560 women (age 53.7 ±11.3 years) selected from a pool of 1,200 women treated at the Fibromyalgia Unit of the Viamed Hospital in Seville, Spain, across 3 years. The study participants, diagnosed with FM according to the American College of Rheumatology (ACR) 2016 criteria, were randomly allocated in two groups: 280 received standard pharmacological treatment and 280 received the same treatment plus eight sessions of LIMS, 20 minutes long, once a week. The variables analyzed were the widespread pain index (WPI), symptoms severity score (SS score) and the Spanish-validated version of the FM impact questionnaire (S-FIQ). The evaluations were performed at the beginning of LIMS treatment and at 2, 12 and 24 weeks after the end of the last LIMS treatment session. From the second week after the last LIMS session, there was improvement ($p < 0.001$) in the variables WPI, SS score and S-FIQ. This improvement was maintained throughout the 24 weeks of monitoring after the last intervention. The age of the patients and the severity of the symptoms at the time of diagnosis did not affect the improvement observed in the three variables studied. The authors concluded that treatment with LIMS for eight weeks resulted in improvement in FM diagnostic variables, which was maintained up to 24 weeks after the last treatment session. Based on the data obtained and the evaluation instruments used, the authors stated that LIMS was an effective therapeutic tool for improving FM symptoms and the impact of this disease on the quality of life of patients, independent of age and degree of pain, and could be recommended as a part of a multimodal approach for FM treatment. This study did not address the physiological effects that underlie the improvement observed in patients. Therefore, further studies that explain the neurophysiological foundations that support the use of this therapy are needed. Other limitations of the study were that anthropometric variables such as weight, fat mass, muscle mass and other behavioral changes or alternative therapies that patients performed during the course of this study, such as physical activity, were not controlled.

In a double-blind, prospective RCT, Karakaş and Gök (2020) studied the efficacy of pulsed electromagnetic field (PEMF) therapy when added to a conventional physical therapy program in reducing pain and functional limitation in patients with chronic non-specific neck pain. The study included 63 patients (15 males, 48 females, age range 25 to 59 years) that were divided into either a PEMF therapy group (n = 33) that received 20 minutes of PEMF in addition to a physical therapy program or a control group (n = 30) that received only the physical therapy program. The groups were similar in terms of demographic and clinical characteristics, and both showed improvement in pain and functionality. The authors

noted that the study limitations included the use of the conventional physical therapy program in both study groups, the lack of monitoring of the use of paracetamol for pain control in the study participants, lack of long-term measurements, the subjective measurement tools used and the heterogeneity of the etiology of neck pain among the participants. They concluded that PEMF is safe in patients with non-specific neck pain, but it is not superior in improving pain and functional limitation and that further large-scale, prospective RCTs using a standard dose of PEMF with a more specific patient sample are needed to demonstrate evidence for the effectiveness of PEMF.

Yang et al. (2020) completed a systematic review of 16 RCTs and a meta-analysis of 15 RCTs to evaluate the effects of PEMF therapy and PEMF parameters on symptoms and quality of life (QOL) in people with osteoarthritis (OA). The total population in the 16 studies was 1078 with 554 in treatment groups and 524 in placebo-controlled groups. Treatment time varied between 10 days and 6 weeks so two different treatment durations (< 4 weeks and 4-6 weeks) were used in the subgroup analysis. The longest follow-up time was 12 weeks. Fourteen of the studies involved OA of the knee while one study included the ankle, two studies addressed OA of the hand and two studies addressed OA of the cervical spine. The authors determined that, compared with placebo, there was a beneficial effect of PEMF therapy on pain and stiffness regardless of the treatment duration while benefit in physical function in people with OA was only seen if the therapy regimen lasted for 4 to 6 weeks. They did not observe any association between PEMF therapy and QOL in people with OA regardless of the length of the treatment program. Limitations noted by the authors included the high levels of heterogeneity across outcome measures, the small number of studies included, the short length of time for the treatment phases (≤ 6 weeks) and follow-up (maximum of 12 weeks) They recommended further studies to explore efficacy with long-term follow-up and to assess the effects of this modality on QOL.

ECRI published a Custom Product Brief (2019) on the SofPulse targeted pulsed electromagnetic field (them) device that is intended to reduce pain and swelling post-operatively. Based on the limited evidence from three very small RCTs on the use of SofPulse following breast surgeries, they concluded that the device may relieve short-term pain, and may reduce (but not eliminate) narcotic use when compared to a sham (placebo) device. The report stated that the evidence is inconclusive as the studies assessed too few patients and that results need to be confirmed in larger, longer-term RCTs examining different surgery types and comparing the device to other pain control methods.

Chen et al (2019) completed a systematic review and meta-analysis evaluating the efficacy of PEMF therapy on pain, stiffness, and physical function in patients with knee osteoarthritis. The review included eight RCTs that that compared PEMF of various parameters and treatment regimens with placebo. The studies involved 421 patients of similar age, sex ratio, and body mass index. All the included studies were determined by the reviewers to have a low or moderate risk of bias. The limitations noted by the authors included the small number of RCTs and sample size available for review, the inclusion of only articles published in English and that there was significant heterogeneity in the meta-analysis of the visual analogue scale (VAS) for pain. The authors concluded that PEMF is beneficial for improving physical function of the knee joint despite not having any advantage in treating pain or stiffness. They recommend further RCTs to confirm their findings and to determine the optimal frequency, intensity, treatment regimen and duration of PEMF therapy.

Newberry et al. (2017) conducted a systematic review to assess the efficacy of a variety of noninvasive interventions [including but not limited to ES techniques (including TENS), NMES, and pulsed electromagnetic field therapy (PEMF)] for OA treatment of the knee. A search was conducted using PubMed, Embase, the Cochrane Collection, Web of Science, the Physiotherapy Evidence Database, ClinicalTrials.gov, and abstracts from professional practice society annual meetings (e.g., American College of Rheumatology, American Academy of Orthopedic Surgery). Eligible studies were those that were RCTs that enrolled adults 18 years or over who were diagnosed with OA of the knee and compared any of the interventions of interest with placebo (sham) or any other intervention of interest that reported a clinical outcome (including pain, function, and quality of life). The investigators also included single-arm and prospective observational studies that analyzed the effects of weight loss in individuals with OA of the knee on a clinical outcome. Findings were stratified according to duration of interventions and outcomes: short term (4–12 weeks), medium term (12–26 weeks), and long term (> 26 weeks). A total of 107 studies were included in the review and of those, 3 studies evaluated treatment with pulsed electromagnetic field therapy. Based on a pooled analysis, PEMF had a statistically nonsignificant beneficial effect on short-term pain. In addition, the investigators reported that the evidence is insufficient to assess the effects of PEMF on short-term or other outcomes, and that larger randomized controlled trials are needed.

Negm et al. (2013) conducted a systematic review and meta-analysis to determine if low frequency (≤ 100 Hz) pulsed subsensory threshold electrical stimulation produced either through pulsed electromagnetic field (PEMF) or pulsed electrical stimulation (PES) vs. sham PEMF/PES intervention is effective in improving pain and physical function at treatment completion in adults with knee OA blinded to treatment. A search was conducted using MEDLINE, CINAHL, EMBASE, CENTRAL and AMED as well as in three clinical trial registries including Clinical Trials Registry, Current Controlled Trials, and the World Health Organization International Clinical Trials Registry Platform. Eligible studies included those with: 1) participants with clinically and/or radiological confirmed knee OA; 2) PEMF/PES frequency was ≤

100 Hz; 3) the comparator was sham PEMF/PES; 4) the primary outcome was pain and/or physical function; 5) the study design was RCT with blinded participants; 6) data for knee OA participants were reported independently pre- and post-treatment; and 7) participants were over 30 years of age. A total of seven RCTs (459 participants/knees) were included. PEMF/PES appeared to improve physical function [standardized mean difference (SMD) = 0.22, 95% CI, 0.04 to 0.41, p = 0.02], and did not reduce pain (SMD = 0.08, 95% CI, −0.17 to 0.32, p = 0.55). The strength of the body of evidence was low for physical function and very low for pain. The authors concluded that current evidence is of low and very low quality suggesting that low frequency (≤ 100 Hz) pulsed subsensory threshold electrical stimulation produced either through PEMF/PES vs. sham PEMF/PES is effective in improving physical function but not pain intensity at treatment completion in adults with knee OA blinded to treatment. The authors also stated that methodologically rigorous and adequately powered RCTs are still needed to confirm and extend the findings of this review.

Farr et al. (2006) reported on a prospective, cohort study examining the use of PES for the treatment of OA of the knee in 288 patients. The device was used for 16-600 days with a mean of 889 hours. Improvement in all efficacy variables was reported. A dose-response relationship between the effect and hours of usage was observed as cumulative time increased to more than 750 hours. Improvements in the patient's or physician's global evaluation of the patient's condition occurred in 59% of patients who used PES less than 750 hours and in 73% of patients who used it more than 750 hours. The lack of a control group weakens the evidence in this study.

Clinical Practice Guidelines

American Academy of Orthopaedic Surgeons (AAOS)

In its clinical practice guideline on non-arthroplasty management of OA of the knee, the AAOS reviewed one high quality study on the use of a wearable PEMF device for pain management in patients with knee osteoarthritis. The Society downgraded their recommendation one level to Limited due to feasibility issues in that PEMF is not widely used in practice settings where patients are treated for knee OA which may limit access for some patients. They recommend continued research with larger RCTs that examine the long-term effectiveness of PEMF and studies that identify factors that distinguish between patients who respond and those who do not respond to PEMF (2021).

Percutaneous Peripheral Nerve Stimulation (PNS)

There is insufficient evidence to support the use of PNS for the treatment of pain. While some studies have compared the effectiveness of PNS to placebo, the overall quality of the evidence is weak and limited. Most of the published studies consist of retrospective reviews, case reports, small case series and small randomized controlled trials. Further large, multi-centered, blinded, long-term RCTs are needed to evaluate the efficacy of PNS. Ongoing studies may provide more definitive evidence of safety and efficacy of PNS.

Gilmore et al. (2023) completed a prospective, multi-center case series of patients with chronic low back pain (CLBP) recalcitrant to multiple non-surgical treatments to illustrate the durability of responses to medial branch PNS. The study included 74 adults (average age 56.3 years, 53% female) who completed their treatment with implanted percutaneous PNS for 60 days. Participants were implanted with the same PNS device then were instructed to use percutaneous PNS for at least six hours per day and up to 12 hours per day for 60 days. They were then followed through 14 months (12 months after the treatment period) to assess responses to pain intensity, disability, pain interference, health-related quality of life, depression, and patient global impression of change. The authors reported that 91% of participants experienced clinically meaningful improvement in at least one outcome after 2 months, 79% at 5 months 73% at 8 months, 75% at 11 months and 77% at 14 months while 77% of participants experienced clinically meaningful improvement in two or more outcomes at 2 months, 63% at 5 months, 60% at 8 months, 58 = 9% at 11 months and 58% at 14 months. Opioid utilization was also noted to be reduced in 15 of the 20 participants who reported taking them at baseline and the reductions in opioid consumption were sustained over the 12-month follow up period with the average consumption reduced from 28.5 mg morphine equivalent (MME) at baseline to 13.4 MME after 2 months of PNS and was further reduced to 5.4 MME at 14 months. Limitations of the study included the lack of randomization to treatment vs. placebo intervention, lack of control of supplemental treatments (such as medications or other therapies), and the heterogeneity of CLBP diagnoses and previous treatments. The authors concluded that treatment of CLBP with 60 days of percutaneous PNS treatment produced clinically meaningful improvements in average pain intensity, disability, and/or pain interference for a majority of participants through the entire 14-month follow-up period.

In their Health Technology Assessment on percutaneous PNS for the treatment of intractable chronic pain in adults, Hayes (2022, updated 2023) identified and reviewed four studies (2 RCTs and 2 prospective pretest-posttest studies) and found that the quality of evidence was very low with two studies deemed fair quality, one poor quality and one very poor quality. The report concluded that these studies suggest that percutaneous PNS may be associated with pain reduction and improvement of quality of life, activities of daily living and medication use rates and appears to be safe; however, the available evidence was insufficient to draw definitive conclusions regarding efficacy and safety. They noted that none of

the four studies included patient sub analysis or regression analyses to inform patient selection criteria and the report recommended additional well-designed studies with larger populations and comparisons with treatment alternatives to strengthen the reliability of the evidence base and to provide greater confidence in the observed trends.

Char et al. (2022) completed a systematic review of 14 prospective studies (including the Gilmore 2019a and Gilmore 2019b studies below) on the efficacy of PNS for neuropathic pain as it relates to pain intensity, neurological deficits, neuropathy, and other secondary outcomes. Three of the studies were RCTs and 11 studies were prospective observational studies/case series. The studies addressed various types of peripheral pain including complex regional pain syndrome (3 studies), phantom limb pain (3 studies), shoulder pain (2 studies), post-surgical pain (2 studies) and mononeuropathies (5 studies), The authors stated that the pooled results demonstrated very low quality or low quality of evidence supporting reduced pain intensity of peripheral neuropathic pain after treatment with PNS for upper or lower extremity neuropathic pain. The authors reported that the majority of patients experienced at least a 30% reduction in pain and that it was common for patients to report greater than 50% pain relief. They also reported that this reduction in pain was consistent across all types of peripheral neuropathic pain syndromes. The authors recommended future prospective, well-powered studies to assess the efficacy of PNS for peripheral neuropathic pain.

Hayes published an Evolving Evidence Review on the SPRINT PNS System and its application for the treatment of chronic pain (2021, updated 2023). The report concluded that, based on a review of published clinical studies, there is minimal support for using this device for treatment of chronic pain. They also noted that there were no published systematic reviews and no published guidelines or position statements specifically addressing Sprint PNS for chronic pain. While Hayes identified 3 newly published studies in the 2023 update, the impact of these studies after their review of the abstracts stated that the new studies were unlikely to change the current level of support of minimal support for the use of the SPRINT PNS System for treatment of chronic pain.

ECRI published a Clinical Evidence Assessment on implantable PNS devices for treating chronic pain (2021) and determined that the evidence is inconclusive due to too few data. The report stated that the studies are at high risk of bias due to various reasons including small sample size, single-center focus, retrospective design, and lack of controls, randomization and/or blinding. The report also stated that the findings may not generalize across patients with different pain etiologies, and they noted that there were no published studies that compared PNS with other chronic pain management methods, such as spinal cord stimulation, transcutaneous electric stimulation, peripheral nerve field stimulation or nerve blocks. The report suggested additional larger RCTs are needed to permit conclusion.

ECRI also published the following reports for PNS for pain: Sprint Peripheral Nerve Stimulation System for Treating Peripheral Nerve Pain (2018, updated 2022), StimRouter Neuromodulation System for Treating Peripheral Nerve Pain (2020), and StimQ Peripheral Nerve Stimulator System for Treating Peripheral Nerve Pain (2018). All of these reports indicate that the evidence is inconclusive since there are too few data.

The Agency for Healthcare Research and Quality (AHRQ) performed a systematic review of 37 RCTs on the comparative effectiveness of 10 interventional therapies for acute and chronic pain for specific conditions. They concluded that the evidence was insufficient to assess peripheral nerve stimulation for upper extremity peripheral neuropathic pain (2021).

In a prospective, multicenter single-arm case series on the effect of PNS on treating chronic axial back pain, Gilmore et al (2021), determined that percutaneous PNS may provide a promising first-line neurostimulation treatment option. The study included 81 participants and was conducted across a variety of clinical care settings. All participants were implanted with percutaneous open-coil PNS leads which were then connected to the SPRINT PNS System. The participants were instructed to use PNS for 6–12 h/day for up to 60 days, after which the leads were withdrawn. No additional interventions apart from percutaneous PNS was provided to any participants for their back pain prior to the primary end point of the study. The authors reported that 57% of the 51 participants who completed a 14-month visit sustained clinically meaningful reductions in average back pain intensity through the 14 months. The authors acknowledged that this was not a randomized trial and that it did not include a control group. They concluded that patients with chronic axial back pain who have failed multiple prior treatments may receive significant benefit from percutaneous PNS. Limitations of the study include the risk of bias due to industry sponsorship.

Helm et al (2021) conducted a systematic review of the effectiveness and safety of PNS for chronic pain that included one RCT of high quality which evaluated the efficacy of PNS on 28 traumatic lower extremity amputees (Gilmore 2019b study below), four RCTs of moderate quality (including Wilson, 2014 reviewed below) and four case series of moderate quality. The studies included in the systemic review evaluated the use of PNS to treat refractory peripheral nerve neuropathic pain (including complex regional pain syndrome, nerve entrapment, and post-stroke pain), cluster headache and pelvic pain. The authors reported that three of the RCTs evaluated relief of peripheral nerve neuropathic pain at a minimum of 3 months, with two showing greater than 50% relief at the end point and the third showing a mean reduction of 27% versus

essentially no relief in the control group. They also found that the case series supported the RCTs, with greater than 50% relief in roughly two-thirds of the patients, although they noted that the studies included in the systematic review lacked sufficient homogeneity to support a meta-analysis. The authors noted that the majority of reviewed studies had small sample sizes and that the systematic review was limited by the paucity of high-quality literature supporting its use. They concluded that PNS requires further research on the efficacy of therapy and on the mode of action to become more widely accepted.

Ilfeld et al. (2021) conducted a multicenter randomized, sham-controlled pilot study to determine the feasibility and optimize the protocol for a subsequent clinical trial and estimate the treatment effect of percutaneous peripheral nerve stimulation on postoperative pain and opioid consumption. Preoperatively, an electrical lead was percutaneously implanted to target the sciatic nerve for major foot/ankle surgery (e.g., hallux valgus correction), the femoral nerve for anterior cruciate ligament reconstruction, or the brachial plexus for rotator cuff repair, followed by a single injection of long-acting local anesthetic along the same nerve/plexus. Postoperatively, participants were randomized to 14 days of either electrical stimulation (n = 32) or sham stimulation (n = 34) using an external pulse generator in a double-masked fashion. The dual primary treatment effect outcome measures were (1) cumulative opioid consumption (in oral morphine equivalents) and (2) mean values of the "average" daily pain scores measured on the 0 to 10 Numeric Rating Scale within the first 7 postoperative days. During the first 7 postoperative days, opioid consumption in participants given active stimulation was a median (interquartile range) of 5 mg (0 to 30) versus 48 mg (25 to 90) in patients given sham treatment [ratio of geometric means, 0.20 (97.5% CI, 0.07 to 0.57); $p < 0.001$]. During this same period, the average pain intensity in patients given active stimulation was a mean ±SD of 1.1 ±1.1 versus 3.1 ±1.7 in those given sham [difference, -1.8 (97.5% CI, -2.6 to -0.9); $p < 0.001$]. The investigators concluded that percutaneous peripheral nerve stimulation reduced pain scores and opioid requirements free of systemic side effects during at least the initial week after ambulatory orthopedic surgery. The limitations of this study include a small sample size and a short follow-up period.

Xu et al. (2021) conducted a systematic review to assess the clinical evidence for PNS in the treatment of acute or chronic pain. Study selection criteria included randomized trials, observational studies, and case reports of PNS used for in acute or chronic pain. Data extraction and methodological quality assessment were performed using Cochrane review methodologic quality assessment and Interventional Pain Management Techniques-Quality Appraisal of Reliability and Risk of Bias Assessment (IPM-QRB) and Interventional Pain Management Techniques-Quality Appraisal of Reliability and Risk of Bias Assessment for Nonrandomized Studies (IPM-QRBNR). The evidence was summarized utilizing principles of best evidence synthesis on a scale of 1 to 5. A total of 227 studies met inclusion criteria and were included in qualitative synthesis. Evidence synthesis based on randomized controlled trials (RCTs) and observational studies showed Level II evidence (evidence obtained from at least one relevant high-quality RCT or multiple relevant moderate- or low-quality RCTs) of PNS for postamputation pain, chronic pelvic pain, chronic low back pain, shoulder pain, and lower extremity pain; and Level IV evidence (evidence obtained from multiple moderate- or low-quality relevant observational studies) in peripheral neuropathic pain and postsurgical pain. A meta-analysis was not possible due to wide variations in experimental design, research protocol, and heterogeneity of study population. According to the authors, there is a lack of high-quality RCTs for the use of PNS. The authors indicated that rigorously designed RCTs are needed to further validate the use of percutaneous PNS for most indications in pain management.

Deer et al. (2020) performed a systematic review of PNS for pain. An international interdisciplinary work group conducted a literature search for PNS. Inclusion criteria included prospective RCTs with meaningful clinical outcomes that were not part of a larger or previously reported group. Excluded studies were retrospective, had less than two months of follow-up, or existed only as abstracts. Full studies were graded by two independent reviewers using the modified Interventional Pain Management Techniques-Quality Appraisal of Reliability and Risk of Bias Assessment, the Cochrane Collaborations Risk of Bias assessment, and the US Preventative Services Task Force level-of-evidence criteria. Peripheral nerve stimulation was studied in 14 RCTs for a variety of painful conditions (headache, shoulder, pelvic, back, extremity, and trunk pain). Moderate to strong evidence supported the use of PNS to treat pain. According to the authors, there was moderate evidence (Level II) that implanted PNS can be expected to provide at least modest improvements in mono-neuropathic pain (Deer et al., 2016) and hemiplegic shoulder pain (Wilson et al., 2014; Wilson et al., 2017). The authors indicated that additional prospective trials could further refine appropriate populations and pain diagnoses.

Gilmore et al. (2019a) conducted a multicenter, double-blinded, randomized, placebo-controlled study to assess the safety and effectiveness of percutaneous PNS for chronic neuropathic pain following amputation. Twenty-eight lower extremity amputees with postamputation pain were enrolled in the study. Subjects underwent ultrasound-guided implantation of PNS leads and were randomized to receive PNS or placebo for 4 weeks. The placebo group then crossed over and all subjects received PNS for four additional weeks. The primary efficacy endpoint evaluated the proportion of subjects reporting ≥ 50% pain reduction during weeks 1-4. A significantly greater proportion of subjects receiving PNS (n = 7/12, 58%, $p = 0.037$) demonstrated ≥ 50% reductions in average postamputation pain during weeks 1-4 compared with subjects receiving placebo (n = 2/14, 14%). Two subjects were excluded from efficacy analysis due to eligibility changes.

Significantly greater proportions of PNS subjects also reported ≥ 50% reductions in pain (n = 8/12, 67%, p = 0.014) and pain interference (n = 8/10, 80%, p = 0.003) after 8 weeks of therapy compared with subjects receiving placebo (pain: n = 2/14, 14%; pain interference: n = 2/13, 15%). The investigators concluded that this study demonstrates that percutaneous PNS therapy may provide enduring clinically significant pain relief and improve disability in patients with chronic neuropathic postamputation pain. Study limitations included small sample size, industry sponsorship short follow-up period (4 weeks.), no significant difference in opioid usage reductions between groups, even though the PNS therapy group had greater absolute and percent reductions in average opioid usage.

Gilmore et al. (2019b) evaluated changes in chronic pain and functional outcomes after amputation up to 12 months as a follow-up to a 60-day PNS treatment (Gilmore et al., 2019a). Significantly more participants in group 1 reported ≥ 50% reductions in average weekly pain at 12 months (67%, 6/9) compared with group 2 at the end of the placebo period (0%, 0/14, p = 0.001). Similarly, 56% (5/9) of participants in group 1 reported ≥ 50% reductions in pain interference at 12 months, compared with 2/13 (15%, p = 0.074) in group 2 at crossover. Reductions in depression were also statistically significantly greater at 12 months in group 1 compared with group 2 at crossover. The investigators concluded that this study suggests that percutaneous PNS therapy delivered over a 60-day period may provide significant carry-over effects including pain relief, potentially avoiding the need for a permanently implanted system while enabling improved function in patients with chronic pain. The investigators indicated that although the pain relief and pain interference outcomes were clinically meaningful and statistically significant, the sample sizes made some outcomes difficult to interpret, such as the trend in both group 1 and group 2 towards greater pain relief during follow-up compared with the end of treatment. The investigators indicated that it is possible that the loss of 4 participants to follow-up influenced the average pain relief at later time points.

Clinical Practice Guidelines

National Institute for Health Care Excellence (NICE)

In its interventional procedures guidance (2022) on neurostimulation of lumbar muscles for refractory non-specific chronic low back pain, NICE concluded that the evidence on the efficacy and safety is limited in quantity and quality. The guideline recommends that neurostimulation of lumbar muscles should only be used with special arrangements for clinical governance, consent and audit or research.

Peripheral Subcutaneous Field Stimulation (PSFS) or Peripheral Nerve Field Stimulation (PNFS)

Evidence on PNFS is limited, consisting of small trials and case studies. More robust prospective controlled trials comparing PSFS or PNFS with placebo or alternative treatment modalities are needed to evaluate the efficacy of this treatment for chronic pain.

Van Heteren et al. (2023) performed a comparative study of the efficacy of spinal cord stimulation (SCS) with the addition of PNFS on pain and quality of life in patients with persistent spinal pain syndrome (PSPS) or failed back surgery syndrome (FBSS) for at least six months and had a pain score on the visual analog scale (VAS) of at least 50 mm for both leg and back pain. The study was based on data from a multicenter RCT and included 100 adults between 18 and 75 years of age. All patients received lead placement and underwent trial stimulation for one week. For those patients who responded to SCS alone with a reduction of back and leg pain by at least 50%, an implantable pulse generator (IPG) was implanted (SCS-only group). In patients with a pain reduction of at least 50% only in their legs, subcutaneous leads were additionally implanted (SCS + PNFS group) and connected to one single IPG. Both groups received optimal pain treatment and were consequently followed per protocol for 12 months after implantation. There were no significant differences in baseline characteristics between the two groups. Outcome measures included pain, quality of life, anxiety and depression, overall health, and disability. Data was reviewed for the 75 patients who completed the 12-month follow-up visit which included 21 from the SCS-only group and 54 from the SCS + PNFS group. The authors reported that both groups showed a significant reduction in back and leg pain at 12 months compared with baseline measurements and that the SCS + PNFS group showed improvements in affective pain ranking index, sensitive pain ranking index, and total pain ranking index whereas there was no significant improvement in these outcomes reported by participants in the SCS-only group. Limitations included the small size of the control group, the retrospective design and lack of blinding. The authors concluded that PNFS in addition to SCS provided equal beneficial long term pain relief and quality-of-life improvements in patients with chronic back and leg pain that was refractory to SCS alone. The authors recommended future research to identify differences in patient characteristics to identify the patients who need SCS alone and those who need SCS with PNFS stimulation.

Rigoard et al. (2021) conducted a randomized controlled trial (RCT) with a 12-month follow-up, to assess the potential added value of peripheral nerve field stimulation (PNfS), as a salvage therapy, in persistent spinal pain syndrome-type 2 (PSPS-T2) patients experiencing a "failed spinal cord stimulation (SCS) syndrome" in the back pain component. Fourteen

patients between February 2013 and April 2017 were enrolled in this study (clinicaltrials.gov: NCT02110888) and randomized into 2 groups ("SCS + PNfS" group/n = 6 vs. "SCS only" group/n = 8). The primary objective of the study was to compare the percentage of back pain surface decrease after 3 months, using a computerized interface to obtain quantitative pain mappings, combined with multi-dimensional SCS outcomes. The authors concluded that back pain surface decreased over a 12-month period from baseline for the "SCS + PNfS" group (80.2% ±21.3%) compared to the "SCS only" group (13.2% ±94.8%) (p = 0.012), highlighting the clinical interest of SCS + PNfS, in cases where SCS fails to address back pain. With paresthesia generated under tonic stimulation, the authors were unable to blind the SCS + PNfS combination. In addition, a small sample size (14 patients) makes it difficult to decide whether these conclusions can be generalized to a larger population. Further investigation is needed before clinical usefulness of this procedure is proven.

In an Evolving Evidence Review on the use of the Bridge device (formerly NSS-2) on alleviating symptoms of opioid withdrawal, Hayes (2021, updated 2023) identified one study for review. While the study indicated the device was effective in alleviating symptoms of opioid withdrawal, it lacked a control group to demonstrate how the efficacy of the device compares with sham devices, pharmacologic treatments, or behavioral interventions. The review noted that there is a comparative study underway with results expected in 2023; however, no newly published studies were found in the 2023 update.

Hayes (2021; updated 2023) published a Health Technology Assessment on the efficacy of using PNFS on adults with nonresponsive refractory chronic low back pain (CLBP) and gave the technology an overall low rating. The initial assessment included six identified studies (including the Verrills and van Gorp studies below): two RCTs, two prospective comparative cohort studies, one prospective pretest-posttest study and one retrospective pretest-posttest study. The 2023 update identified four newly published studies (one RCT, two comparison studies, and one prospective pretest-posttest study); however, after their review of the study abstracts, Hayes stated that these studies were unlikely to change their current position. The comparisons included sham, optimal medical management, and the use of PNSF with spinal cord stimulation(SCS) vs. SCS alone. Overall, the evidence suggested that PNFS is safe for use in the selected adult population; however, the overall body of evidence was considered by the authors to be of very low quality due to small sample sizes, heterogeneity of comparators, inconsistency in treatment procedures across the studies, limited follow-up data and individual study limitations. The Hayes assessment noted that this treatment approach is not curative as it only temporarily relieves pain and dysfunction for only while the device is implanted and functioning. The duration of pain relief needs further investigation as does identifying specific patient selection criteria to determine who might benefit from this procedure, to determine the long-term efficacy and safety of PNFS versus comparable therapies and definitive alternatives.

In a follow up to their 2016 multicenter RCT below, van Gorp et al. (2019) continued with an open phase part of the study where all participants received optimal spinal cord stimulation (SCS) and PNFS simultaneously for treatment of low back pain due to failed back surgery syndrome (FBSS). Outcome data were collected from the 50 participants by analyzing their questionnaires using multilevel regression models at 12 months and compared with the data collected at baseline. The authors found improvement in all secondary measurements including functional capacity and in overall quality of life to be statistically significant. They noted that more than 40% of the participants reported a reduction of back pain ≥ 50%. The authors concluded that PNFS in addition to SCS provides a statistically significant and relevant relief of low back pain in FBSS patients in whom SCS alone is only effective for relief of leg pain. They noted that the study is limited due to the controlled part of the study only lasting for three months, that the study could not be blinded and that the study combined participants from both arms into the analysis. They recommend future studies to target optimization of the technique and pattern analysis.

Eldabe et al (2019) conducted the SubQStim study, a prospective multicenter RCT to compare the effectiveness of PNFS (referred to as subcutaneous nerve stimulation (SQS) in this study) plus optimized medical management (OMM) to OMM alone in people with back pain due to failed back surgery syndrome (FBSS). There were 116 participants recruited from 21 centers, which was short of the goal of 314 evaluable subjects due to the sponsor ending the study because of prolonged recruitment challenges. In the first phase of the trial, 56 participants were randomized to receive PNFS plus OMM and 60 received OMM only for nine months. Due to early study termination, participants were not able to complete the study and attend all visits as they were discontinued at various time points; in all, 74 participants were able to complete the nine-month primary endpoint visit. The authors recognized that the study had a few potential limitations. First, there was a lack of blinding as insertion of the PNFS was a surgical intervention. Second, that participants in the study could be considered as having already failed OMM by definition of FBSS which may predispose those in the OMM alone arm to not experience significant improvement. Third, the decision to end the study early resulted in a smaller number of participants contributing to the data analysis and affected the study’s ability to inform on the long-term effectiveness of PNFS. The authors concluded that, despite early termination of the study, the addition of PNFS to OMM was clinically and statistically more effective than OMM alone in relieving low back pain at up to nine months.

The study by van Gorp et al. (2016) was a multicenter, RCT investigating the efficacy of subcutaneous stimulation (SubQ) as ADD-ON therapy to traditional spinal cord stimulation (SCS) in treating back pain in failed back surgery syndrome patients. Individuals with a minimal pain score of 50 on a 100 mm VAS for both leg and back pain were eligible. If pain reduction after trial SCS was ≥ 50% for the leg but < 50% for the back, patients received additional SubQ leads and were randomized in a 1:1 ratio in a study arm with subcutaneous leads switched on (SubQ ADD-ON), and an arm with subcutaneous leads switched off (Control). The primary outcome was the percentage of the patients, at 3 months post-implantation, with ≥ 50% reduction of back pain. A total of 97 patients were treated with SCS for leg and back pain. Of these, 52 patients were randomized and allocated to the Control group (n = 24) or to the SubQ ADD-ON group (n = 28). The percentage of patients with ≥ 50% reduction of back pain was significantly higher in the SubQ ADD-ON group (42.9%) compared to the Control group (4.2%). Mean VAS score for back pain at 3 months was a statistically significant 28.1 mm lower in the SubQ ADD-ON group compared to the Control group. The authors concluded that subcutaneous stimulation as an ADD-ON therapy to SCS is effective in treating back pain in failed back surgery syndrome patients where SCS is only effective for pain in the leg.

McRoberts et al. (2013) conducted a multi-site, 2-phase, crossover RCT evaluating the safety and efficacy of PNFS in 44 patients with localized chronic intractable pain of the back. During phase I, patients rotated through 4 stimulation groups (minimal, subthreshold, low frequency, and standard stimulation). If a 50% reduction in pain was achieved during any of the 3 active stimulation groups (responder), the patient proceeded to phase II, which began with implant of the permanent system and remained in place for 52 weeks. The primary endpoint was a reduction in pain, assessed by the VAS. Of the 44 patients enrolled, 30 completed phase I. Twenty-four patients were classified as responders in phase I, and 23 received permanent system placement. Significant differences in VAS scores were observed between baseline and all follow-up visits during phase II. The authors concluded that PNFS is safe and effective as an aid in the management of chronic, localized back pain. Limitations to this trial are small study group size.

Yakovlev et al. (2011) conducted a case series study to evaluate PNFS as an alternative treatment option for patients with post-laminectomy syndrome when conventional treatments did not provide adequate relief of intractable LBP. Eighteen patients underwent an uneventful PNFS trial with percutaneous placement of 4 temporary quadripolar leads. The leads were placed subcutaneously over the lumbar or thoraco-lumbar area. The temporary leads were removed when patients experienced excellent pain relief over the next 2 days. The patients were then implanted with permanent leads. All patients reported sustained pain relief 12 months after implantation. The authors concluded that PNFS may be more effective in treating intractable LBP than SCS in patients with post-laminectomy syndrome after multilevel spinal surgeries. The lack of a control group limits the validity of the conclusions of this study.

Verrills et al. (2011) evaluated the clinical outcomes of 100 consecutive patients receiving PNFS for chronic pain in a prospective, observational study. The patients received PNFS for the treatment of chronic craniofacial, thorax, lumbosacral, abdominal, pelvic, and groin pain conditions. Overall, 72% of patients reduced their analgesic use following PNFS. Patients receiving a lumbosacral PNFS for chronic LBP reported a significant reduction in disability following treatment, as determined by the Oswestry Disability Index. No long-term complications were reported. The authors concluded that PNFS can be a safe and effective treatment option for intractable chronic pain conditions. This study was not randomized or controlled.

To aid in alleviating symptoms associated with opioid withdrawal, a PNFS delivery system known as the Bridge device (formerly known as the NSS-2 Bridge) is marketed for use as a non-pharmacologic component of an inpatient or outpatient detoxification treatment program. One single-arm retrospective pilot study has been published (Miranda and Taca, 2017), citing 64 of 73 patients successfully transitioning to medically-assisted treatment after using the device with no reports of AEs. While several guidelines on the management of opioid withdrawal are available, none addressed the use of this type of device for this indication. Prospects for the Bridge System are unclear at this time (Hayes, 2021).Other FDA approved PNFS systems similar to the Bridge are the DrugRelief® stimulator and the Sparrow Therapy System™. These auricular neurostimulation devices are also used to reduce the symptoms of opioid withdrawal during detoxification. At present, there are no studies or published literature relating to these devices. More information on these devices can be found using Product Code PZR on the following FDA website: 510(k) Premarket Notification (fda.gov). Accessed August 30, 2023.

Microcurrent Electrical Nerve Stimulation Therapy (MENS)

MENS therapy has been studied in several small RCTs and case series for conditions such as delayed onset muscle soreness (Curtis et al. 2010) and diabetes, hypertension, and chronic wounds (Lee, et al. 2009). None of these studies are large, controlled trials designed to test the effectiveness of MENS therapy against a placebo device. Therefore, due to the limited evidence in the peer reviewed literature, conclusions cannot be reached regarding the safety, efficacy, or utility of MENS therapy to decrease pain and/or facilitate healing for any condition.

Bavarian et al. (2021) conducted a systematic review and meta-analysis on the efficacy of MENS in treating masticatory myofascial pain. Four RCTs were included in the qualitative systematic review with a pooled total of 159 participants, while three of the studies (pooled total of 140 participants) had sufficient raw data to be included in the quantitative meta-analysis. The primary outcome measured was relief of pain assessed by any validated scale, such as the visual analog scale (VAS) or numeric verbal pain rating scale. All of the articles included MENS being compared to a control group for the treatment of myofascial pain of the masticatory muscles. The authors determined that three of the four studies were judged to be at low risk of bias with the fourth study deemed as having a high risk of bias. The authors determined that there was a modest reduction in pain score in patients receiving MENS with an increased mean reduction of pain by an additional -0.57 points on the VAS. The authors concluded that the meta-analysis showed that MENS was an effective, non-invasive treatment for reducing pain in patients with myofascial pain of the masticatory muscle. Limitations noted by the authors included the small number of studies available for analysis, the heterogeneity of the study designs, inconsistent reporting of quantitative data and inconsistencies in control groups. This review included the Zuim 2006 study that was previously included in this policy.

A systematic review and meta-analysis completed by Iijima and Takahashi (2021) determined that microcurrent therapy (MCT) significantly improved shoulder pain and knee pain compared with sham MCT without any severe adverse events. Their review included four RCTs and five non-RCTs that studied the effectiveness of MCT for treating neck pain (1 non-RCT), shoulder pain (1 RCT), elbow pain (1 non-RCT), low back pain (1 RCT and 2 non-RCTs) and knee pain (including the Lawson and Ranker RCTs below and 1 non-RCT). No serious adverse events requiring medical treatment were reported among the 281 pooled participants. The authors also stated that placebo response may be joint- or disease-dependent and that sham MCT may elicit a clinically beneficial response in subacute to chronic knee pain as was supported by the high quality of evidence established by using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) with high reproducibility using the Template for Intervention Description and Replication (TIDieR) checklist. The authors noted that their review was limited by only having a single reviewer rather than the preferred independent review by 2 reviewers, that their review did not include studies where MCT was compared with other treatment approaches and that the small number of included studies limited their analysis so generalizability could not be addressed. They suggested future research include high-quality clinical trials for shoulder pain and low back pain as well as the treatment effects of MCT on pain from multiple sites, and studies on the mechanism of MCT itself.

Lawson et al (2021) conducted a randomized, double-blinded, placebo-controlled clinical trial to determine if microcurrent therapy increased function and decreased pain in people with acute knee pain. The study was conducted in their university laboratory and in the homes of the 52 self-referred study participants. The participants were randomized into the treatment group (n = 26) or the placebo-control group (n = 26). Participants wore the electrodes with the active or placebo microcurrent treatment for three consecutive hours per day and abstained from pain or anti-inflammatory medications throughout the four-week study. Daily text reminders were sent to use the device. This method demonstrated high compliance as it required participants to respond with an affirmative response or repetitive reminder texts would be sent until confirmation of compliance was achieved. The authors reported the study showed a trend in increased function that correlated well with a decrease in pain, especially in the 3rd week, and decreased effusion on musculoskeletal ultrasound imaging over the first two weeks in the active MENS group versus the placebo group. Limitations noted by the authors include the small number of participants, the use of the Lower Extremity Function Scale (LEFS) as it appeared to not be sensitive enough in this population to capture changes in function, and the lack of long-term follow-up. They concluded that MENS decreased knee pain and increased function and that it may be an alternative or be used with a pharmacological approach for people with acute knee pain. The authors recommend future studies evaluate the effect MENS has on edema via musculoskeletal ultrasound elastography, the effect different dosages of MENS have in the perception of specific acute knee pain and function, longer term follow-up to observe post-treatment effect of MENS on pain, function, muscle or edema and the effect of MENS on chronic knee pain especially around knee osteoarthritis.

A retrospective, case-control study by Shetty et al (2020) showed that a higher percentage of adult patients treated in their facility with adjuvant frequency-specific microcurrent (FSM) in addition to physical rehabilitation for low back pain (LBP) had significantly improved pain and disability when compared to patients in a control group who chose not receive FSM. In their study, they retrospectively reviewed data from the records of 213 patients (167 with LBP and 46 with neck pain) who received FSM in addition to their personalized therapy program along with the records of 78 patients (61 with LBP and 17 with neck pain) who only received their personalized therapy program. Each patient's rehabilitation protocol was varied and personalized based on their severity of pain and response to movement testing. All patients underwent a minimum rehabilitation treatment of 30 days and a maximum of 90 days with a minimum of 6 supervised physiotherapy sessions at the clinic. The authors concluded that the use of adjuvant FSM therapy along with active rehabilitation significantly reduced pain and disability when compared to patients treated with active rehabilitation alone for low back pain; however, the addition of FSM to therapy did not appear to significantly affect clinical outcomes of pain and disability in patients with neck pain. The authors noted that their study was limited by its retrospective design, the reporting period for results of 90 days did not reflect medium- and long-term implications of adjuvant FSM therapy, and the study

measurements did not consider the effect of neurophysiological and psychosocial factors. They recommend future well-designed, placebo controlled randomized trials to confirm the benefits of adjuvant FSM therapy for treating LBP or neck pain.

In a single-center, four-arms, double-controlled pilot RCT, Ranker et al (2020) evaluated the potential effects of MET on pain in patients with knee osteoarthritis (OA), to explore effects of different treatment parameters and to distinguish these effects from placebo-effects. The study included 52 participants who were randomized into four groups: MET with 100 µA (n = 14), MET with 25 µA (n = 13), a sham treatment group (n = 12), and a control group with no intervention (n = 13). In the intervention groups, all participants received 10 treatment sessions total given over a three-week period. The participants and therapists were blinded to the treatment allocation. The authors observed that evening pain was reduced significantly in the groups that received MET compared to the sham and control groups. They also found that the difference between the sham group and the control group was not significant and that all but the sham group improved in activities of daily living. They concluded that MET has beneficial effects on pain in people with OA that are not explained by a placebo effect; however, they also recognized that further confirmation is needed before recommendations can be given. Limitations of the study that were noted by the authors included the lack of systematic tracking of additional therapies during the study and of self-medication of analgesics that could bias the results.

Kwon et al. (2017) conducted a prospective, double-blinded, sham-controlled RCT to evaluate the effects of short-term MENS on muscle function in the elderly. A total of 38 healthy elderly participants aged 65 years and above were enrolled and randomly divided into a real MENS or a sham MENS stimulation group. Both groups received stimulation to the 8 anatomical points of the dominant arm and leg during the course of 40 minutes. The authors report that their hypothesis was accurate that real MENS was superior to sham in enhancing muscle function in healthy elderly subjects following short term application. Limitations to this study included the lack of definition of the “healthy elderly,” short application time of the MENS, and lack of follow-up evaluation. Long-term RCTs with follow-up assessments are needed to confirm these results.

Gossrau et al. (2011) conducted a single-blinded, placebo-controlled randomized trial to assess the efficacy of MENS for reduction of painful diabetic neuropathy (PDN) in 41 patients. Participants were divided into 2 groups: 22 treated with MENS therapy and 19 with placebo. Treatment plan was 3 therapy sessions per week for 4 weeks. Primary outcomes measured included pain intensity, pain disability, and QOL at baseline, and the end of treatment, and 4 weeks post-treatment using standardized questionnaires. Patients with a minimum of 30% reduction in neuropathic pain score (NPS) were defined as therapy responders. After 4 weeks, only 6 of 21 patients in the study group (30%) responded to MENS therapy versus 10 of 19 (53%) of the placebo group. The differences in Pain Disability Index (PDI) for both groups were not statistically significant. The authors concluded that MENS therapy for PDN is not superior to placebo.

Percutaneous Electrical Nerve Stimulation (PENS)

While some studies have compared the effectiveness of PENS to placebo, the overall quality of the evidence is weak and quite limited as published studies have included small patient populations and short-term follow-ups. Further robust studies are needed to evaluate the efficacy of this therapy for chronic pain.

In a single-center, prospective RCT that evaluated the safety and effectiveness of transcutaneous electrical acupoint stimulation (TEAS) in postoperative analgesia following pediatric orthopedic surgery, Li et al. (2023) reported that those patients who received TEAS experienced significantly less postoperative pain and had reduced consumption of perioperative analgesia following surgery. The study included 58 children aged 3-15 years who were scheduled to undergo a lower extremity orthopedic procedure under general anesthesia. All of the children in the study had a TEAS stimulator connected but TEAS was only applied to the 29 children randomly assigned to the active group. The 29 children in the sham group did not receive TEAS therapy but the rest of the enhanced recovery after surgery (ERAS) protocol was applied. For those in the active group, the acupoints were stimulated starting from 10 minutes before anesthesia induction until completion of the surgery. Pain intensity was measured with the Faces Pain Scale-Revised (FPS-R) which was assessed in the post-anesthesia care unit and at 2 hours, 24 hours, and 48 hours postoperatively. The authors reported that the FPS-R scores in the TEAS group were significantly decreased before leaving the PACU and at 2 hours and 24 hours postoperatively. They also reported that the incidence of emergence agitation, intraoperative use of remifentanil, and time to extubation were significantly lower in the TEAS group. The authors also reported that the time to first press of the patient-controlled intravenous analgesia (PCIA) pump was also significantly longer, and the pressing times of the PCIA pump in 48 h after surgery was significantly decreased in the TEAS group. The authors concluded that TEAS may safely and effectively relieve postoperative pain and minimize perioperative analgesic use in children undergoing lower extremity orthopedic surgery.

Beltran-Alacreu et al (2022) conducted a systematic review and meta-analysis to determine if the use of PENS is more effective when compared to TENS for the reduction of musculoskeletal pain intensity in adults. The study included nine

RCTs (n = 563) in the qualitative analysis, and seven RCTs (n = 527) in the quantitative analysis. All of the studies compared the effect of PENS versus TENS with four of the studies including either a sham or placebo group. Six of the studies had a parallel design and the other three were cross-over studies. While the search period ended on December 31, 2020, the most recent study included in the review and meta-analysis was published in 2012. Participant diagnoses included low back pain (LBP; n = 254), chronic neck and shoulder pain (n = 90), sciatica (n = 64), knee osteoarthritis (n = 24), and chronic musculoskeletal pain (n = 131). Pain was the main outcome assessed [via the Visual Analog Scale (VAS) and the numerical pain rating scale] and the follow-up period ranged from 24 hours to 8 months. Protocols and parameters for PENS and TENS application were heterogeneous among the studies. The authors reported that there was a significant improvement in pain intensity, medication use and quality of life in favor of PENS with a low recommendation level per GRADE guidelines, while there was a moderate recommendation level supporting no differences when TENS and PENS were used for pain intensity when only the three studies with a lower risk of bias were analyzed. The authors concluded that there was low quality of evidence for more pain intensity reduction with PENS, but the difference was not clinically significant and that, based on their findings, the authors do not recommend the use of PENS in a clinical setting as the first treatment step.

Wang et al. (2022) conducted a systematic review and meta-analysis of RCTs to evaluate the effectiveness and safety of transcutaneous electrical acupoint stimulation (TEAS) in treating post-operative pain. The study included 16 RCTs with 1,305 participants divided into the TEAS group (n = 651, 49.8%) and or the control group (n = 651, 50.1%) who had undergone a minimally invasive or open surgical procedure. All of the studies utilized the visual analogue scale (VAS) within 24 hours after surgery to measure the primary outcome with secondary outcomes including postoperative opioid analgesic drug consumption and notation of any adverse reactions (nausea, vomiting, or dizziness) within 24-72 hours of the surgical procedure. Quality assessment of the included studies (as reported by the authors) resulted in 7 trials being classified as low risk of bias, 8 as unclear risk of bias, and 1 as high risk of bias. The meta-analysis on the efficacy and safety of TEAS for treating postoperative pain included data from 12 of the RCTs with 1019 participants, of which 511 of them were in the control group and 508 were in the TEAS intervention group. The authors reported that the VAS scores were significantly decreased in the TEAS group after surgery at 24 hours and the incidence of postoperative nausea, vomiting and dizziness was significantly lower in the TEAS group at 24-72 hours. Postoperative opioid analgesics were also reported by the authors to be reduced in the TEAS group within 72 hours after surgery. The authors concluded that TEAS can reduce postoperative pain, analgesic utilization, and adverse reactions after surgery and that it is a reasonable modality to incorporate into a multimodal management approach for postoperative pain.

Hayes reported in an Evidence Analysis Research Brief (2022) on the use of PENS for the treatment of low back pain (LBP) that there were no relevant newly published studies that met the inclusion criteria since they published their Health Technology Assessment (HTA) on the subject in 2017 and archived it in August, 2021. In the 2017 HTA, Hayes identified 3 clinical studies that evaluated the safety and efficacy of PENS for chronic LBP and found that the body of evidence was of very-low-quality and was insufficient to make a definitive conclusion about PENS as monotherapy or in combination with physical therapy in patients with chronic LBP. The HTA noted that the results suggested a short-term (3 months) benefit in pain and pain-related disability from baseline; however, these differences were typically statistically but not clinically significant.

In a multicenter RCT, Gao et al (2021) assessed the preventive effectiveness of transcutaneous electrical acupoint stimulation (TEAS) on postoperative paralytic ileus (POI) after colorectal surgery. The study included 610 participants from 10 hospitals who were randomly allocated into the TEAS group or a sham group with 307 patients allocated to the sham group and 303 patients to the TEAS group. All participants, the researchers, surgeons, and anesthesiologists were blinded to the study group allocation. TEAS treatment or sham was administered in the PACU and once a day for the first three postoperative days. The authors found that TEAS lowered the incidence of postoperative paralytic ileus following colorectal surgery by 8.7% and decreased the risk of postoperative paralytic ileus by 32%. They also noted that TEAS enhanced gastrointestinal functional recovery with shortened recovery time to flatus, defecation, normal diet, and bowel sounds. No statistically significant difference was found in the 30-day postoperative complication rate or with the total length of stay between the TEAS and sham groups. The authors noted that the study was limited by the fact that the participants could not be blinded to the treatment due to the nature of the intervention itself, that the efficacy of reducing POI after other kinds of surgery is unknown, that the study excluded participants with prophylactic ileostomy due to the difficulties in evaluating for flatus, that the block randomization methodology may not have completely avoided the violation of allocation concealment and that the study was not undertaken in combination with a comprehensive Enhanced Recovery After Surgery (ERAS) program. They recommend future studies to assess the long-term surgical outcomes when TEAS is included in the treatment protocol.

Chen et al. (2020) conducted a meta-analysis of 14 RCTs with 1653 participants (835 received TEAS in experimental group, 818 received sham TEAS in control group) to evaluate the effectiveness of transcutaneous electrical acupoint stimulation (TEAS) for preventing postoperative nausea and vomiting (PONV) after general anesthesia. The authors

reported no publication bias was detected and that the meta-analysis showed that the addition of TEAS to postoperative care resulted in lower incidence of PONV, fewer patients needing antiemetic rescue, lower incidence of dizziness and pruritis compared with controlled intervention. They concluded that TEAS is a reasonable modality to incorporate into a multimodal management approach for the prevention of PONV, postoperative nausea, postoperative vomiting. They stated that their findings should be interpreted with caution because of the limitations in the meta-analysis which include that the specific mechanism of TEAS is not clear and limits the promotion of its use, that 12 of the studies were conducted in China where the technique may be more popular, the small sample sizes (< 100 participants) in all of the studies, short-term follow-up with symptoms only being recorded within 24 hours after surgery. The authors recommend more studies to focus on the long-term effect of TEAS on PONV and relevant outcomes, and whether TEAS could prevent PONS secondary to other types of anesthesia beyond general anesthesia.

To evaluate the effects of PENS alone or as an adjunct with other interventions on pain and related disability in musculoskeletal pain conditions, Plaza-Manzano et al (2020) conducted a systematic review and meta-analysis of 19 parallel or cross-over RCTs with various musculoskeletal conditions with short- or midterm follow-ups. They found most studies to be of high methodological quality except for three that were considered poor quality and that most the trials were biased due to the inability to blind the therapists and participants; however, in general, the risk of bias of the trials in the meta-analysis was low. The authors concluded that there was a low level of evidence indicating the effects of PENS alone had a large effect compared with sham and a moderate effect when compared with other interventions for decreasing pain intensity at short term. The authors acknowledged that the systematic review and meta-analysis were limited by the number of RCTS looking at the effect of PENS on specific musculoskeletal pain conditions was small, that the method of evaluation of PENS varied and that the results of some of the RCTs were inconsistent and unprecise. They recommended well-designed RCTS to examine the effect of PENS alone or in combination with other therapeutic interventions with long-term follow-up periods and that the trials be designed to compare the effect of real vs. sham PENS as well as the most appropriate treatment parameters and anatomical locations to create reproducible results.

In a single-center, double-blind RCT, Kong et al (2020) evaluated the effect of electroacupuncture (EA) on pain severity in adults with chronic low back pain (CLBP). The study included 121 adults who were randomized into either a treatment group (n = 59) or a sham (n = 62) group and then treated by one of 10 acupuncturists for 12 sessions of real or placebo (sham) electroacupuncture administered twice a week over 6 weeks. Outcome measures were collected, and participants were followed for two weeks beyond completion of the six-week treatment protocol. The authors found no significant difference in CLBP scores between real and sham electroacupuncture treatment; however, post hoc analyses did find a significant treatment effect of EA in reducing disability associated with CLBP. They stated that the finding of an association between positive coping strategies and functional improvement that was seen on both the univariate and multivariate analyses is unique to the study. The authors also found that the White race was associated with worse outcomes in pain and felt that the racial influence may be caused by differences in cultural backgrounds in that participants with backgrounds that include traditional Chinese medicine may be more likely to respond to acupuncture. Limitations they noted included that the study does not quantify the specific effect of EA vs manual acupuncture, that there was missing blinding data due to implementation imperfections and that the outcome collection spanned a total of only 10 weeks. The authors recommend larger studies with multicultural samples and testing the interaction between cultural background and treatment allocation, as well as collecting longer-term outcomes.

Meng et al. (2018) conducted a multicenter RCT to investigate the effects of electroacupuncture (EA) on reducing inflammatory reaction and improving intestinal dysfunction in patients with sepsis-induced intestinal dysfunction with syndrome of obstruction of the bowels. A total of 71 patients were randomly assigned to control group (n = 36) and treatment group (n = 35). Patients in the control group were given conventional therapies including fluid resuscitation, anti-infection, vasoactive agents, mechanical ventilation, supply of enteral nutrition, and glutamine as soon as possible. In addition to conventional therapies, patients in treatment group underwent 20 minutes of EA twice a day for 5 days. At baseline, day 1, day 3, and day 7 after treatment, biomarkers assessing intestinal inflammation and dysfunction were measured and recorded, respectively. Additionally, days on mechanical ventilation (MV), length of stay in intensive care unit (ICU), and 28-day mortality were also recorded. The authors concluded that EA, as a supplement to conventional therapy, can reduce inflammatory reaction and has protective effects on intestinal function than conventional therapy alone in patients with sepsis-induced intestinal dysfunction with syndrome of obstruction of the bowels. However, there were no significant differences identified between the 2 groups relative to number of days on MV, length of stay in ICU, and 28-day mortality. Limitations to this study include small sample size and single-center investigation. Further studies are required.

Mi et al. (2018) conducted a randomized observational trial to evaluate the effect of transcutaneous electrical acupoint stimulation (TEAS) on dosages of anesthetic and analgesics as well as the quality of recovery during the early period after laparoscopic cholecystectomy. One hundred patients who underwent laparoscopic cholecystectomy with grade I and II of the American Society of Anesthesiologists criteria were evenly and randomly assigned into an observation group and a

control group. The patients in the observation group were treated with TEAS from 30 minutes prior to anesthesia induction to the end of operation. The patients in the control group received stimulation electrode(s) in the corresponding points without ES for the same time period. Researchers concluded that TEAS could reduce the dosage of anesthetic and analgesic delivered intraoperatively, as well as improve the quality of recovery during the early period after laparoscopic cholecystectomy.

Rossi et al. (2016) conducted a multicenter, prospective, observational study to evaluate the short- and long-term efficacy of a single probe and single shot PENS approach to treat chronic neuropathic pain. Seventy-six patients affected by neuralgia were enrolled in the study and divided into 3 groups depending on the etiology of the neuralgia (21 herpes zoster infection, 31 causalgia, 24 postoperative pain). In the study, Numerical Rating Scale (NRS) and Neuropathic Pain Scale (NPS) were assessed at baseline, 60 minutes after PENS, 1 week, and 1-, 3-, and 6-months post-therapy. Perceived health outcome was measured with Euroqol-5-dimension (EQ-5D) questionnaire at baseline and at 6 months. Pain assessment ratings decreased significantly after 60 minutes of PENS therapy and the reduction remained constant throughout the follow up period. Perceived health outcome measured with EQ-5D increased significantly from baseline. The authors concluded that PENS therapy produced significant and long-lasting pain relief in chronic peripheral neuropathic pain of different etiologies. The study limitations included small sample size, non-randomized observational study, short follow up period, and high prevalence of post-herpetic and occipital neuralgias.

Clinical Practice Guidelines

American Academy of Orthopaedic Surgeons (AAOS)

In the updated evidence-based clinical practice guideline on non-arthroplasty management of osteoarthritis of the knee, the AAOS reviewed one high quality study and downgraded their recommendation one level to Limited due to feasibility issues. The authors noted that PENS is feasible but requires a practitioner trained in PENS which may limit access for some patients. The guideline stated that continued research with larger RCTs that examine the long-term effectiveness of PENS is needed and that the studies that identify responders and non-responders to PENS would also be important (2021, updated 2022).

National Institute for Health and Care Excellence (NICE)

NICE updated their guidance on the use of TENS, percutaneous electrical nerve simulation (PENS) and IFT for managing low back pain with or without sciatica and stated that these modalities should not be offered for treatment of low back pain with or without sciatica due to the paucity of evidence available that included mostly small individual studies of low or very low quality. No clinical benefit was found for PENS on improving pain and function when compared to usual care in a mixed population of people with or without sciatica. Clinical benefit for pain and function was observed at less than four months but no clinical benefit was found after 4 months. The Guideline Development Group GDG) noted that, although there was evidence in places positive for people with low back pain, it was of low quality with low patient numbers. It was also noted that PENS is not widely used so a recommendation for its use would be a significant change in practice. The GDG concluded that there was insufficient evidence of clinical benefit to support a recommendation for the use of PENS for low back pain or sciatica (2016, updated 2020).

In 2013, NICE published guidance related to the use of PENS to control neuropathic pain. The guidance states, “The current evidence on the safety of PENS for refractory neuropathic pain raises no major safety concerns and there is evidence of efficacy in the short term.” Therefore, this procedure may be used with normal arrangements for clinical governance, consent, and audit. The guideline also indicates that NICE encourages further research into PENS for refractory neuropathic pain, particularly to provide more information about selection criteria and long-term outcomes, with clear documentation of the indications for treatment.

American Academy of Neurology (AAN), American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM), American Academy of Physical Medicine and Rehabilitation (AAPMR)

In a joint guideline report on the treatment of painful diabetic neuropathy (PDN), the AAN, AANEM, and AAPMR concluded that PENS should be considered for the treatment of PDN (Bril et al., 2011).

Percutaneous Electrical Nerve Field Stimulation (PENFS)

While some studies have compared the effectiveness of PENFS to placebo, the overall quality of the evidence is weak and quite limited as published studies have included small patient populations and short-term follow-ups. Further robust studies are needed to evaluate the efficacy of this therapy for chronic pain.

In a single-center, open-label prospective clinical trial, Karrento et al. (2023) evaluated the effects of PENFS on pain, common comorbidities, and quality of life in children with cyclic vomiting syndrome (CVS). The study included 30 children (60% female), 8-18 years old, with drug refractory CVS. Each participant completed surveys at the beginning, at week six and at extended follow-up approximately 4-6 months later. Surveys included the Abdominal Pain Index (API), State-Trait Anxiety Inventory for Children (STAI-C), Pittsburgh Sleep Quality Index (PSQI), and Patient Reported Outcome Measurement Information System (PROMIS) Pediatric Profile-37. Each participant wore the PENFS device for five days (24 hours/day) for six consecutive weeks of auricular PENFS. The authors reported that the frequency of episodes/month decreased from a monthly median of 2.0 episodes/month at baseline to 0.5 episodes/month at the extended follow-up. The authors also reported that the median API scores, and STAI-C scores decreased from baseline to week six and to extended follow up while short-term improvements in sleep were seen at 6 weeks, but not at extended follow up. Quality of life (QOL) measures including physical function, anxiety, fatigue, and pain interference were also reported by the authors to have improved short-term with long-term benefits noted only for anxiety. Limitations of the study include the single-center design, lack of randomization and blinding, small sample size, and the lack of objective assessment tools. The authors concluded that auricular neurostimulation using PENFS is effective for pain and several disabling comorbidities, including anxiety, sleep and several aspects of QOL in children with CVS.

Woodbury et al. (2022) conducted a randomized controlled trial (RCT) to evaluate changes in cortical thickness and right posterior insula (r-pIns) gamma-aminobutyric acid (GABA) concentrations in veterans with fibromyalgia treated with auricular percutaneous electric nerve field stimulation (PENFS). This study was an open label investigation conducted in a government hospital. Twenty-one veterans with fibromyalgia were randomized to receive either standard therapy (ST; i.e., 4 weekly visits with a pain practitioner) or ST with auricular PENFS (ST + PENFS). Neuroimaging data was collected at baseline (i.e., before the first treatment session) and again within 2 weeks post-treatment. Clinical pain and physical function were also assessed at these timepoints. Single-voxel magnetic resonance spectroscopy was conducted in r-pIns to assess changes in r-pIns GABA concentrations and high-resolution T1-weighted images were collected to assess changes in regional gray matter volume using cortical thickness. Both the ST + PENFS and ST groups reported a decrease in pain with treatment. Volumetric: Cortical thickness decreased in the left middle posterior cingulate ($p = 0.018$) and increased in the left cuneus ($p = 0.014$) following ST + PENFS treatment. These findings were significant following false discovery rate (FDR) correction for multiple comparisons. ST group right hemisphere insula cortical thickness increased post-treatment and was ($p = 0.02$) inversely correlated with pain scores. ST + PENFS group right hemisphere posterior dorsal cingulate size ($p = 0.044$) positively correlated with pain scores. GABA: There were no correlations with GABA, though a trend was noted towards increased GABA following treatment in both groups ($p = 0.083$) using a linear mixed effects model. The authors concluded that the results suggested a novel effect of PENFS reflected by differential volumetric changes compared to ST. The changes in GABA that occurred in both groups were more likely related to ST. Insular GABA and cortical thickness in key regions of interest may be developed as potential biomarkers for evaluating chronic pain pathology and treatment outcomes. The GABA analysis was limited by a small number of MRI acquisitions meeting criteria for GABA spectroscopy fit error ($n = 9$ for PENFS with ST, and $n = 4$ for ST alone). While initial results concerning this non-pharmacologic treatment for fibromyalgia are promising, the clinical efficacy of PENFS for fibromyalgia should be explored in larger, randomized, double-blind, placebo-controlled trials.

An Evolving Evidence Review by Hayes (2022, updated 2023) on the use of IB-Stim for the treatment of pain associated with irritable bowel syndrome in adolescents stated that there is no/unclear support of the use of this device for this indication based on a review of full-text clinical studies. The review consisted of one fair-quality (refer to the Kovacic (2017) study below) that did not compare IB-Stim to any other active treatment. They did not identify any systematic reviews nor any relevant guidelines that addressed the use of IB-Stim for this clinical indication.

ECRI (2021) published a Clinical Evidence Assessment on the IB-Stim device (Innovative Health Solutions) that is intended to treat adolescents (aged 11 to 18 years) with abdominal pain related to irritable bowel syndrome (IBS). The authors identified a single, published post hoc subgroup analysis of adolescents with IBS who were included in the IB-Stim pivotal trial that compared the efficacy of the device in a sham-controlled trial with 27 adolescents who received IB-Stim treatment with 23 adolescents who received sham stimulation. This study suggested that IB-Stim reduces abdominal pain more than sham stimulation by 3-week follow-up, but that benefits were not sustained through 12-week follow-up. The authors excluded the pivotal trial itself from the Assessment because it included pooled outcomes from patients with other gastrointestinal disorders as well as IBS. The authors stated that the major limitations of the post hoc analysis were that it does not permit conclusions because of the design of the pivotal study itself, that the subgroup analysis compromised the pivotal study's randomization because the randomization was not stratified by patient condition, the analysis had a small sample size, a single center design and a lack of published independent studies to validate the findings. They also noted the post hoc analysis had a high risk of bias which rendered the evidence inconclusive. The authors recommended RCTs comparing IB-Stim with pharmacotherapy and other noninvasive pain management techniques in adolescents and reporting on patient-oriented outcomes to address evidence gaps.

Kovacic et al. (2017) conducted a single center, blinded, sham RCT evaluating the efficacy of a PENFS device known as Neuro-Stim (Innovative Health Solutions, Versailles, IN) in adolescents with abdominal pain-related functional gastrointestinal disorders. Adolescents (aged 11-18 years) who met Rome III criteria with abdominal pain-related functional gastrointestinal disorders were enrolled and assigned to either PENFS (n = 60) with an active device or sham (n = 55). After exclusion of patients who discontinued treatment (1 in the study group, 7 in the sham group) and those who were excluded after randomization because they had organic disease (2 and 1 in the study and sham groups, respectively), 57 patients in the PENFS group and 47 patients in the sham group were included in the primary analysis. The primary efficacy endpoint was change in abdominal pain scores measured via the Pain Frequency-Severity-Duration (PFSD) scale. Patients in the PENFS group had greater reduction in worst pain compared with sham after 3 weeks of treatment. Participants from each group (n = 10) discontinued the study due to side-effects, none of which were serious. Symptoms included ear discomfort, adhesive allergy, and syncope due to needle phobia. The researchers concluded that PENFS with Neuro-Stim is has sustained efficacy for abdominal pain-related functional gastrointestinal disorders in adolescents. Study limitations include small sample size and short follow up period and exclusions after randomization.

Restorative Neurostimulation

There is insufficient evidence in the published peer reviewed scientific literature to support the efficacy of restorative neurostimulation for the treatment of chronic low back pain. Additional larger studies comparing restorative neurostimulation to standard of care and current alternative treatments are needed to demonstrate safety and efficacy for this modality.

Ardeshiri et al. (2022) recruited 44 consecutive patients with refractory, predominantly nociceptive axial chronic low back pain (CLBP) to participate in a single-center, consecutive cohort study to evaluate the effectiveness of restorative neurostimulation to improve pain, disability and quality of life. Median age of the participants was 54 years and median duration of CLBP was 5.8 years. The study participants had no history of surgical intervention for CLBP prior to being implanted with a neurostimulation device. All surgeries were performed by a single surgeon. Data were obtained from the ReActiv8 Post Market Surveillance Registry (ReActiv8-C) in consecutive patients with untreated back pain from a single center with 1 year of clinical follow-up. Outcome measures for pain (numeric rating scale), disability (Oswestry Disability Index), and quality of life (5-level EuroQol 5-Dimension) were collected at baseline and 3, 6, and 12 months after activation. Forty (91%) of the 44 patients completed follow-up after 1 year of therapy; 2 patients withdrew from the study before completing 1 year of therapy, and 2 patients were unable to attend follow-up appointments due to the COVID-19 pandemic. The authors reported that 68% of patients had moderate (≥ 30%) reductions in pain, 52% had substantial (≥ 50%) reductions in pain, and 48% were remitters and had a pain score ≤ 3, which is considered to be mild pain to pain-free after 1 year of therapy. No lead migrations were reported; however, one patient required revision due to lead fracture. The authors concluded that clinically meaningful improvements in pain, disability and quality of life were achieved with restorative neurostimulation and that this therapy is a new treatment option for well-selected patients with refractory CLBP.

Hayes (2022) completed a Health Technology Assessment on the use of PNS for the treatment of chronic pain in adults refractory to conservative management. The assessment included a review of the four eligible studies that they found which consisted of 2 RCTs and 2 prospective pretest-posttest studies with follow-up periods of 6 months to 1 year. The report noted an overall very low-quality body of evidence with 2 fair-quality studies, 1 poor-quality study and 1 very poor-quality study which leaves the observed trends of benefit that were observed in the four studies relatively unsubstantiated. Limitations of the four studies included the heterogeneity of the study designs, the small sample sizes, patient attrition, and insufficient follow-up time. Hayes concluded that the small, very low-quality body of evidence suggests that PNS may be associated with pain reduction and improvement in quality of life, activities of daily living and medication utilization

In an Evolving Evidence Review focusing on the ReActiv8 Implantable Neurostimulation System, Hayes (2022, updated 2023) completed a review of full-text clinical studies and found minimal support for using ReActiv8 for chronic low back pain (CLBP). They found one fair-quality RCT (Gilligan, 2021 below) that compared ReActiv8 active treatment to sham that reported only marginal benefits to pain, disability, and quality of life (QOL) in patients with CLBP. They also found one prospective pretest-posttest study (Deckers 2018 below) that compared ReActiv8 with baseline and reported statistically and clinically significant improvements in pain, disability, and QOL. Hayes did not find any studies that compared ReActiv8 with an active comparator, nor did they find any systematic reviews addressing this device nor any clinical guidelines that addressed the use of ReActiv8 for CLBP. The Evolving Evidence Review did identify two clinical studies that are in progress that will provide more evidence regarding the clinical effectiveness of ReActiv8 when results are published. In the 2023 update, two additional abstracts were identified (including one open-label follow-up from a randomized controlled trial and one prospective single-arm study) but Hayes did not perform a formal review of the full text of these studies.

In a prospective, observational follow-up study of 204 implanted trial participants of the ReActiv8-B trial, Gilligan et al. (2022) evaluated the three-year effectiveness and safety of the ReActiv8 Implantable Neurostimulation System in patients with refractory, disabling chronic low back pain (CLBP). Data was collected using the low back pain visual analog scale (VAS), Oswestry Disability Index (ODI), EuroQol quality of life survey, and through assessment of the participant's opioid intake at baseline, six months, and one, two, and three years after activation. There were 45 participants who were withdrawn from the study after device removal (22%) and another 10 participants who were withdrawn due to loss to follow up (5%). The authors collected data from 133 of the participants and noted that 16 of the participants were not able to keep their three-year follow-up due to coronavirus disease restrictions but remain available for future follow-up. They reported that a total of 62% of participants had a ≥ 70% VAS reduction, and 67% reported CLBP resolution (VAS ≤ 2.5cm); 63% had a reduction in ODI of ≥ 20 points; 83% had improvements of ≥ 50% in VAS and/ or ≥ 20 points in ODI, and 56% had these substantial improvements in both VAS and ODI. A total of 71% (36/51) participants on opioids at baseline had voluntarily discontinued (49%) or reduced (22%) opioid intake. The authors concluded that 83% of participants experienced clinically substantial improvements in pain, disability, or both at three years and that the results of their study showed durable, statistically significant, and clinically substantial benefits in a cohort of patients with severe, disabling CLBP and multifidus muscle dysfunction who were refractory to conservative care. Limitations of the study include the small sample size, high attrition rate, and a lack of follow-up with those participants who underwent removal of the device.

ECRI (2021, updated 2023) published a Clinical Evidence Assessment focused on the safety and effectiveness of the ReActiv8 Implantable Neurostimulation System for the treatment of chronic low-back pain that does not respond to conservative treatment in patients who are not surgical candidates for spinal procedures. The assessment included studies of any design that reported on clinical outcomes of multifidus stimulation with ReActiv8 in patients with chronic low-back pain. In the initial review, the researchers found two studies to review, including the Gilligan 2021 study below and one prospective, multicenter pre-post study. They found that each of the studies had three or more of the following limitations, which result in a high risk of bias: small sample size, no control group, lack of data on comparisons of interest such as other pain management techniques, short follow-up times and/or active sham was used in the study. There were five additional studies identified in the 2023 update including one RCT and 4 before-and-after studies. The RCT studied pain relief at 120-day follow-up and the researchers found that the between group difference in pain relief between the treated group and the sham group at the 120-day follow up was too small to determine if it was clinically important and did not permit conclusions. The review of the four before-and-after studies suggested there was pain relief and functional status benefits with the use of ReActiv8 treatment but the studies were found by ECRI to be at high risk of bias due to the lack of control groups and small study populations. The authors concluded that the evidence remains inconclusive due to too few data on outcomes.

Results of an ongoing follow-up of the ReActiv8-A clinical trial were published by Mitchell, et al. (2021) to document the longitudinal benefits of receiving long-term restorative neurostimulation in patients with intractable chronic low back pain (CLBP). This clinical trial was a prospective, single-arm study at nine sites in the United Kingdom, Belgium and Australia that included 53 patients with disabling CLBP with no indications for spine surgery or spinal cord stimulation and failed conventional management including at least physical therapy and medications. The study population had an average age of 44 ±10 years who had experienced back pain for 14 ±11 years. Stimulation parameters were programmed 14 days post implantation and patients were given instructions to activate the device for 30 minutes twice each day. The participants were then followed at 45, 90, 180, and 270 days, then annually for 48 months. Over the four years of follow-up, one patient was lost to follow-up, 11 exited the study following explant without clinical benefit, four exited following explant with clinical benefit and one exited because of a device migration that could not be repositioned. Thirty-four of the initial 53 patients completed the 48-month follow-up. The authors reported that, initially, patient compliance was relatively high with 84.5% ±22.6% of the maximum number of therapy sessions being completed; however, four years after implantation, patient compliance was at 48.8% ±34.0%, or completion of approximately half of maximum number of stimulation sessions. The authors reported that mean improvements from baseline were statistically significant and clinically meaningful for all follow-ups. They concluded that participants with disabling intractable CLBP who received long-term restorative neurostimulation retained treatment satisfaction and improvement in pain, disability, and quality-of-life through four years. Limitations include the small number of participants, the high attrition rate, the single-arm design, and lack of follow-up for the participants who exited the study.

Gilligan et al (2021) conducted a randomized double-blinded, sham-controlled clinical trial at 26 specialist pain centers to determine the safety and efficacy of an implantable, restorative neurostimulator, the ReActiv8 Implantable Neurostimulation System. This study included 240 participants with refractory mechanical chronic low back pain (LBP) with an impaired multifidus control who continued with LBP despite > 90 days of medical management and at least one attempt of physical therapy. The participants were implanted and randomized using a permuted block scheme for each investigational site to the therapeutic group (n = 102) or the sham control group (n = 102). All participants received stimulation, either therapeutic or low-level sham, twice a day for 120 days. After the primary endpoint, all reported

outcomes were unblinded and all participants received therapeutic stimulation. All study participants were evaluated through 1 year for long-term outcomes and adverse events. The authors reported that 64% of participants had a 50% or greater improvement in their LBP, mean disability improved by 51% from borderline “severe” to “minimal” and that 18 of the 65 participants who were on opioids at baseline discontinued their use. They also reported a 4% serious adverse events rate, including 6 pocket infections requiring system removal. The authors concluded that this study provided important insights and design considerations for future neuromodulation trials.

Scrambler Therapy (ST)

There is insufficient evidence in the published peer reviewed scientific literature to support the efficacy of scrambler therapy/ transcutaneous electrical modulation pain reprocessing (TEMPR) therapy. Studies comparing TEMPR to conventional treatment options and to sham therapy are lacking.

The aim of the meta-analysis done by Jin et al. (2022) was to investigate the efficacy of ST for the management of chronic pain. The study included 7 RCTs with 287 adult patients (142 were in the intervention group and 145 were in the control group) who experienced chronic pain for more than three months. Pain conditions included in the studies were chemotherapy-induced peripheral neuropathy (CIPN) in four trials, postsurgical neuropathic pain, post-herpetic neuralgia, and pain due to spinal stenosis each in two trials, and cancer pain and persistent nonspecific low back pain each in one trial. Comparison groups received various other treatments including sham stimulation, conventional medicine, active comparator, or no treatment. Treatment sessions were between 30 to 50 minutes each over 10 working days and the follow-up periods ranged from 10 days to 3 months from baseline. The authors reported that ST marginally decreased pain scores after the end of the treatment period when compared to the control group and a subgroup analysis found that the use of ST significantly reduced analgesic consumption compared to the control group. The authors noted that there was no significant efficacy observed in the subgroup meta-analyses by methodological quality, type of diseases causing pain, and follow-up period. Limitations included the small sample sizes of the RCTs, the low methodological quality, the heterogeneity of the devices used (first generation versus second generation), the heterogeneity of the study designs, and the inclusion of multiple different causes of chronic pain. The authors concluded that ST appeared to be effective in the management of patients with chronic pain; however, they recommended further large RCTS to confirm their findings.

Kashyap et al. (2022) conducted a randomized controlled trial (RCT) to evaluate the efficacy of scrambler therapy (ST) for enhancing quality of life (QOL) in cancer patients through minimizing pain and opioid intake. A total of 80 patients with head, neck and thoracic cancer were included in the study. In both arms, patients were given pain management drugs following the World Health Organization (WHO) analgesic ladder for ten consecutive days. ST was given each day in the intervention arm. Pain, morphine intake, and QOL (WHOQOL-BREF) were assessed. All domains of QOL improved in the intervention arm in comparison to the control arm. In comparison to baseline, pain improved in both the intervention and the control arm on day 10 and at follow-up. However, QOL significantly improved in the intervention arm, while morphine intake decreased. In the control arm, QOL deteriorated, while morphine intake increased. The authors concluded ST improved QOL. Since the increase in QOL took place along with a lower morphine intake, the improvement in QOL may not only be explained by lower pain scores but, also, by a reduced intake of morphine, because the lower dosages of morphine will decrease the likelihood of side effects associated with the drug. Further research with randomized controlled trials is needed to validate these findings.

Lee et al. (2022) conducted a prospective, double-blinded, randomized controlled trial (RCT) to evaluate the clinical usefulness of scrambler therapy (ST) and identify the pain network alterations associated with ST for chronic neuropathic pain caused by burns. This study (ClinicalTrials.gov: NCT03865693) included 43 patients who were experiencing chronic neuropathic pain after unilateral burn injuries. The patients had moderate or greater chronic pain (a visual analogue scale (VAS) score of ≥ 5), despite treatment using gabapentin and other physical modalities, and were randomized 1:1 to receive real or sham ST sessions. The ST was performed using the MC5-A Calmare device for ten 45 min sessions (Monday to Friday for 2 weeks). Baseline and post-treatment parameters were evaluated subjectively using the VAS score for pain and the Hamilton Depression Rating Scale; MRI was performed to identify objective central nervous system changes by measuring the cerebral blood volume (CBV). After 10 ST sessions (two weeks), the treatment group exhibited a reduction in pain relative to the sham group. Relative to the pre-ST findings, the post-ST MRI evaluations revealed decreased CBV in the orbito-frontal gyrus, middle frontal gyrus, superior frontal gyrus, and gyrus rectus. In addition, the CBV was increased in the precentral gyrus and postcentral gyrus of the hemisphere associated with the burned limb in the ST group, as compared with the CBV of the sham group. Thus, a clinical effect from ST on burn pain was observed after 2 weeks, and a potential mechanism for the treatment effect was identified. The authors concluded these findings suggest that ST may be an alternative strategy for managing chronic pain in burn patients. Limitations include small sample size (43 patients) and short duration of follow-up (2 weeks).

Wang et al. (2022b) conducted a systematic review to evaluate the best available evidence regarding the use of non-invasive neuromodulation techniques for managing chemotherapy-induced peripheral neuropathy (CIPN). A systematic

literature search of the following databases from their inception to October 17, 2021, was performed and was updated on March 2, 2022: AMED via Ovid, CINAHL via the EBSCO Host, Cochrane Library, Embase, PEDro, PubMed, and Web of Science. Randomized controlled trials (RCTs) and quasi-experimental studies examining the safety, feasibility, and efficacy of non-invasive neuromodulation techniques for managing established CIPN were identified. Narrative synthesis was used to analyze data collected from the included studies. Nine RCTs and nine quasi-experimental studies were included. A variety of non-invasive peripheral and central neuromodulation techniques were investigated in those studies, including scrambler therapy, electrical stimulations, photo biomodulation, magnetic field therapy, therapeutic ultrasound, neurofeedback, and repetitive transcranial magnetic stimulation. The authors stated that non-invasive neuromodulation techniques for the management of established CIPN were generally safe and feasible. The efficacy of peripheral neuromodulation techniques such as scrambler therapy and transcutaneous electrical nerve stimulation was mostly unsatisfactory, while central neuromodulation techniques such as neurofeedback and repetitive transcranial magnetic stimulation were promising. The authors concluded the use of non-invasive neuromodulation techniques for managing CIPN, such as scrambler therapy, was still in its early stages. The stated non-invasive central neuromodulation techniques have significant potential for relieving chronic pain and neuropathic symptoms related to CIPN, meriting further exploration. The heterogeneity of the included studies prevented the conducting of a pooled analysis of data from those studies. Therefore, the overall effect of the neuromodulation techniques for managing CIPN could not be estimated. Further research with randomized controlled trials is needed to validate these findings.

A systematic review was conducted by Karri et al. (2022) to summarize the available evidence regarding the use of scrambler therapy (ST) in treating chronic pain syndromes, as well as its analgesic benefits, adverse effects, procedure-specific variables, and other metrics such as sensorimotor tests, medication reduction, and effect on circulation neuropeptides. Two review authors, independently and in a standardized, unblinded fashion, conducted a systematic review to identify relevant studies and extract the necessary outcome measures by surveying multiple data sources from January 1950 through October 2021. A conservative search strategy was implemented to identify all ST studies for the treatment of chronic pain syndromes. Primary outcome parameters collected were analgesic benefit, adverse effects, and other metrics such as sensorimotor testing. A total of 21 studies met the final criteria for study inclusion and comprised randomized controlled trials (n = 8), prospective observational studies (n = 10), and retrospective cohort studies (n = 3). Nearly all the reported studies explored the use of ST for the treatment of neuropathic pain, with chemotherapy-induced peripheral neuropathy being the most studied condition. Most studies were limited by small cohorts but reported ST being safe, well tolerated, and providing clinically meaningful pain reduction. The duration of post-treatment follow-up ranged from ten to 14 days (concordant with completion of typical ST protocols) to three months. Secondary benefits such as medication reduction and improvement of sensory and motor symptoms were noted by some studies. The authors concluded that ST was a safe intervention with potential for analgesic benefit for neuropathic pain conditions. Although the available evidence was most robust for treating chemotherapy-induced peripheral neuropathy, ST was also shown to be effective in treating other neuropathic pain syndromes. Evidence for ST use in nociceptive pain conditions was limited but appears promising. The favorable safety profile and increasing evidence basis for ST warrant more extensive recognition and consideration for use in clinical care. Limitations to this study included performance and detection biases and several included studies reported industry affiliations with the ST manufacturer of the device, and the inventor of the ST device himself was an author of several of the included studies. Further investigation is needed before clinical usefulness of this procedure is proven. The Kashyap and Bhatnagar (2020) study and the Compagnone and Tagliaferri (2015) studies that were previously included in this policy were included in this systematic review.

Hayes (2020, updated 2023) conducted a systematic review to evaluate evidence on the use of scrambler therapy (ST), also referred to as Calmare Pain Therapy and transcutaneous electrical modulation pain reprocessing, for the management chronic pain not related to cancer or cancer treatment. The initial literature search identified 9 relevant clinical studies that met inclusion criteria: 2 RCTs, 1 quasi-RCT, and 6 single-arm studies, including 1 repeated measures time series, 3 pretest/posttest studies, and 2 retrospective database reviews. Hayes noted that a majority of these studies had limited follow-up of ≤ 6 months, making it hard to evaluate long-term effects of ST and that the generalizability of the results was unclear because of the varied treatment regimens across studies and heterogeneity of pain etiologies in the evaluated populations. With their 2023 update, Hayes identified 2 newly published studies; however, they determined that neither of these would result in a change in their findings, which included that the body of evidence, which was considered low or very low quality, is insufficient to draw conclusions regarding the efficacy, and safety of ST for the management of chronic pain not related to cancer or cancer treatment in adults. Hayes continues to recommend that additional large, well-designed clinical studies are needed to evaluate the comparative and long-term effectiveness and safety of ST, and to delineate patient selection criteria.

Clinical Practice Guidelines

American Society of Clinical Oncology (ASCO)

In the updated evidence-based clinical practice guideline by Loprinzi et al (2020) on the prevention and management of chemotherapy-induced peripheral neuropathy (CIPN) in survivors of adult cancers, the ASOC reviewed two randomized trials evaluating scrambler therapy. The Guideline stated that, outside the context of a clinical trial, no recommendation for its use in the treatment of CIPN could be made due to low strength of evidence and low benefits. The authors noted that, while the evidence suggested a potential for benefit from scrambler therapy, larger sample-sized definitive studies are needed to confirm efficacy and clarify risks.

European Society for Medical Oncology (ESMO), European Oncology Nursing Society (EONS), European Association of Neuro-Oncology (EANO)

In a joint ESMO/EONS/EANO Clinical Practice Guideline by Jordan et al. (2020) that addresses the diagnosis, prevention, treatment, and follow-up of chemotherapy induced peripheral neurotoxicity (CIPN), scrambler therapy is not recommended to treat CIPN due to small, randomized trials with inconsistent effectiveness outcomes. The guideline graded scrambler therapy with a D rating, indicating that there is moderate evidence against efficacy or for adverse outcome, and that this treatment approach is generally not recommended.

Translingual Stimulation (TLS)

There is insufficient evidence in the published peer reviewed scientific literature to support the efficacy of translingual stimulation. Robust studies evaluating the long-term safety and efficacy of TLS to treat gait disorders secondary to multiple sclerosis, cardiovascular accident and traumatic brain injury are lacking.

ECRI published a Clinical Evidence Assessment on the Portable Neuromodulation Stimulator™ (PoNS) device and its safety and efficacy for treating chronic balance deficits due to neurologic disorders. The PoNS device is a portable, non-implantable neuromuscular electrical stimulation (NMES) device with a mouthpiece that sends NMES to the dorsal surface of a patient's tongue. The Assessment included three RCTs and 1 non-randomized controlled study and concluded that the evidence was inconclusive due to too few data on the safety and efficacy of PoNS. The authors noted that the same research center that developed the PoNS device directed the three RCTs. They determined that the RCTs had a low risk of bias though because of the way that the trials blinded the participants, trainers and investigators; however, the non-randomized controlled study had a high risk of bias due to the lack of randomization and blinding. The authors noted that PoNS with physical therapy appeared to improve gait and balance in people with mild-to-moderate traumatic brain injury and that it may also benefit those with MS and cerebral palsy; however, the authors recommended additional studies to confirm the results and to determine how long improvements last (2021).

Multiple Sclerosis (MS)

Leonard et al. (2017) completed a pilot study of the effects of noninvasive tongue stimulation using the PoNS device combined with intensive cognitive and physical rehabilitation on working memory, gait, balance, and concomitant changes in the brain. Their study included 14 patients with MS who were randomly assigned to a PoNS stimulation group (n = 7) or to a sham PoNS™ stimulation group (n = 7). At the end of the study, participants in the sham group were offered the opportunity to use the PoNS device, and five individuals returned and completed the active training. The authors concluded that there were significant effects of interventions across the wide range of cognitive domains both in the active and in the sham groups, although there was a trend of greater improvement in the active group. The data demonstrated an improvement over time following PoNS training for both the active and for the rollover group suggesting that the training can have a positive effect on balance in patients with MS. The authors noted that a major shortcoming of the study was the low number of participants in each group and recognized the need for a larger study that balances disease duration across groups.

In a randomized, double-blind, controlled pilot trial of PoNS, Tyler et al. (2014) evaluated the effect of targeted physical therapy with and without non-invasive neuromodulation to improve gait in chronic MS. The study included twenty chronic MS patients with an identified gait disturbance who were randomly assigned by the primary investigator to either an active group (n = 10) that received electrical stimulation on the tongue or to a control group (n = 10) that used a device that did not provide a physiologically significant stimulation on the tongue. The participants and the therapists were blinded as to which group the participant was assigned. Both groups completed a 14-week therapy program with a standardized combination of exercise and the PoNS device that provided electrical stimulation to the tongue. The authors noted that all participants appeared to demonstrate improvements initially, but only the active group continued to improve over the length of the study. Data showed that participants who trained using exercise only without stimulation (control group) continued to improve for the first month at home and then exhibited a plateau or even a decrease in performance. The authors concluded that the active group showed statistically greater improvement in gait than the control group and that

non-invasive electro tactile stimulation, when combined with targeted physical therapy exercises, can significantly reduce clinical symptoms of gait dysfunction in multiple sclerosis.

Traumatic Brain Injury (TBI)

Hou et al. (2022) conducted a clinical investigative study to evaluate the effectiveness of translingual neural stimulation (TLNS) on patients with mild-to-moderate traumatic brain injury (mmTBI) and related brain connectivity using a resting-state functional connectivity (RSFC) approach. This study is part of the long-term clinical trial (NCT02158494), which was completed to investigate the efficacy of translingual neural stimulation (cranial nerve noninvasive neuromodulation). Nine participants with mmTBI were included in the study (43-62-years-old; mean age was 53.11 ±6.60; three males and six females). Their mmTBI occurred at least 1 year before enrollment. Participants had previously participated in physical therapy, had reached a plateau in their functional recovery. Their mmTBI diagnoses were made according to the guidelines established by the Veterans Affairs/Department of Defense. All participants could independently walk for at least 20 minutes and had no medication changes for at least 3 months before the experiment. They were without other medical problems such as oral health, diabetes, hypertension, chronic infectious disease, or other potentially confounding neurological disorders. Resting-state images with 5-min on GE750 3T scanner were acquired from all participants with mmTBI. Paired t-test was used for calculating changes in RSFC and behavioral scores before and after the TLNS intervention. The balance and movement performances related to mmTBI were evaluated by Sensory Organization Test (SOT) and Dynamic Gait Index (DGI). Compared to pre-TLNS intervention, behavioral changes in SOT and DGI were observed. The analysis revealed increased RSFC between the left postcentral gyrus and left inferior parietal lobule and left Brodmann Area 40, as well as the increased RSFC between the right culmen and right declive, indicating changes due to TLNS treatment. However, there were no correlations between the sensory/somatomotor (or visual or cerebellar) network and SOT/DGI behavioral performance. The authors concluded this study presents evidence that TLNS effectively improves balance and movement in mmTBI patients accompanied by increased involvement of neural regions associated with gait, balance, and motor control, and is therefore an effective approach to treating the symptoms of mmTBI patients. A small sample size makes it difficult to decide whether these conclusions can be generalized to a larger population. Further research is needed to determine the clinical relevance of these findings.

Ptito et al (2021) conducted a multicenter RCT with 122 adults, aged 18-65, to assess the safety and efficacy of translingual neurostimulation (TLNS) in patients with a chronic balance deficit who had received physical therapy following a mild to moderate TBI (mmTBI) and had plateaued in recovery. TLNS was delivered through the portable neuromodulation stimulator (PoNS). Randomized participants received PT plus either high-frequency pulse (active therapy; n = 59) or low-frequency pulse (control group; n = 63) TLNS during a 5-week treatment program. All participants followed the same TLNS use and PT regimen with a customized training intensity that was based on the individual's presentation and abilities. Adherence was monitored and verified through the TLNS device automatically by logging usage and showed overall compliance was a mean of 94% across weeks 2 through 5 of the study. The authors noted that participants in both the active and the control group had significant and clinically meaningful improvements in sensory organization test composite score and the dynamic gait index. They noted that the results of this study are limited by the small sample size, the fact that there were two times more female to male participants which is not consistent with the incidence of TBI in the general population, and that there was great variability in previous therapy programs which may have influenced the efficacy of the physical therapy program in the study. The authors concluded that the combination of TLNS plus targeted PT resulted in significant improvements in balance, gait, and sleep quality, in addition to reductions in the frequency of headaches and falls.

Tyler et al (2019) conducted a single-site, double-blind RCT to compare the efficacy of the dosage of high- and low-frequency noninvasive portable neuromodulation stimulator (PoNS) plus targeted physical therapy for treating chronic balance and gait deficits in participants with mmTBI. In their study, 44 participants (18-65y) were randomized 1:1 into either a high-frequency pulse (HFP) group or a low-frequency pulse (LFP) group. All participants received TLNS (HFP or LFP) with PT for a total of 14 weeks (2 in clinic, 12 at home), twice daily followed by another 12 weeks without treatment. The authors found that both groups had a significant improvement in balance, gait, and sleep quality along with reduction in headache severity and frequency. They also found that the improvements were sustained through the 12 weeks after discontinuing TLNS and that results between the groups did not differ significantly from each other. Limitations identified by the authors include the inherent variable presentation of TBI, differences in the nature of mmTBI, participant age, symptom number and severity, time since injury, age at time of injury and degree of success with prior therapy programs might have influenced the variability seen with each assessment. They also noted that there was variability in each participant’s physical, cognitive, and emotional capacity for the training program as well as the impact of the placebo effect, Hawthorne effect, and nonspecific attention and care on study outcomes. The authors recommended future research to assess the dosing parameters of TLNS, a well as additional and longer-term benefits of this treatment.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Functional Electrical Stimulation (FES) Devices

Products used for FES are extensive. Refer to the following website for more information and search by either product code GZI or product name in device name section: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed August 30, 2023)

Neuromuscular Electrical Stimulation (NMES) for Muscle Rehabilitation Devices

Products used for NMES for muscle rehabilitation are extensive. Refer to the following website for more information and search by either product code IPF or product name in device name section: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed August 30, 2023)

Interferential Therapy (IFT) Devices

Products used for IFT are extensive. Refer to the following website for more information and search by either product code LIH or product name in device name section: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed August 30, 2023)

Pulsed Electrical Stimulation (PES) Devices

There are multiple products used for PES. Refer to the following website for more information and search by product name in device name section: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed August 30, 2023)

Percutaneous Peripheral Nerve Stimulation (PNS)

There are several devices used for PNS such as the StimRouter Neuromodulation System, SPRINT PNS System, and StimQ Peripheral Nerve Stimulator System. Refer to the following website for more information and search by either product code NHI or product name in device name section: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed August 30, 2023)

Peripheral Subcutaneous Field Stimulation (PSFS) or Peripheral Nerve Field Stimulation (PNFS) Devices

PSFS or PNFS using a fully implantable system is not currently approved by the FDA. Refer to the following website for more information: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed August 30, 2023)

The Bridge System (previously, the NSS-2 System), a PNFS system marketed as an aid to reduce the symptoms of opioid withdrawal, was FDA approved on November 15, 2017 (Product Code PZR). Refer to the following website for more information: https://www.accessdata.fda.gov/cdrh_docs/pdf17/DEN170018.pdf. (Accessed August 30, 2023)

The DrugRelief® auricular stimulator, a PNFS system marketed as an aid to reduce symptoms of opioid withdrawal, was FDA approved on May 2, 2018 (Product Code PZR). A newer version, the DrugRelief® v1, with an extended shelf life from 6 to 12 months was approved on June 6, 2022. This newer version is otherwise Identical to the predicate in that both devices are body-worn, have identical indications for use and deliver electrical stimulation therapy as an aid in the reduction of opioid withdrawal symptoms. Both devices deliver biphasic electrical stimulation waveforms hence are charge balanced due to the positive and negative phase between active electrode(s) and the ground electrode. Refer to the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K173861. (Accessed August 30, 2023)

The Sparrow Therapy System™ is a transcutaneous auricular neurostimulation device that was FDA approved on January 2, 2021 (Product Code PZR) to be used in patients experiencing opioid withdrawal in conjunction with standard of care for opioid withdrawal symptoms under the supervision of trained clinical personnel. Refer to the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K201873. (Accessed August 30, 2023)

Microcurrent Electrical Nerve Stimulation Therapy (MENS) Devices

MENS devices are categorized as TENS devices intended for pain relief. Refer to the following website for more information and search by Product Code GZJ with specific product name in device name section: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed August 30, 2023)

Percutaneous Electrical Nerve Stimulation (PENS) or Percutaneous Electrical Nerve Field Stimulation (PENFS)

The FDA regulates PENS stimulators as class II devices (Product Code NHI). Several PENS devices have been approved by the FDA. Refer to the following website for more information and search by product name in device name section: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed August 30, 2023)

The IB-Stim, a PENFS system intended for use with functional abdominal pain associated with irritable bowel syndrome (IBS) in patients 11-18 years of age, was FDA approved on June 7, 20019 (Product Code QHH). Refer to the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/denovo.cfm?ID=DEN180057. (Accessed August 30, 2023)

The Deepwave Percutaneous Neuromodulation Pain Therapy System received FDA 510K approval on April 27, 2006 (Product Code NHI) as a PENS device used for the treatment of pain. Refer to the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K061166. (Accessed August 30, 2023)

Restorative Neurostimulation

Restorative neurostimulation devices are categorized as implanted neuromuscular stimulators for lower back muscles. The ReActiv8 Implantable Neurostimulation System was granted premarket approval on June 16, 2020. The device is indicated for bilateral stimulation of the L2 medial branch of the dorsal ramus as it crosses the transverse process at L3 as an aid in the management of intractable chronic low back pain associated with multifidus muscle dysfunction, as evidenced by imaging or physiological testing in adults who have failed therapy including pain medications and physical therapy and are not candidates for spine surgery. Refer to the following website for more information using Product Code QLK: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm. (Accessed August 30, 2023)

Scrambler Therapy (ST)

The Calmare®/ST MC-5A TENS Device was initially approved by the FDA on February 20, 2009. A second 510(k) clearance was issued on May 22, 2015, for the ST MC-5A Device which has also been replaced by the Scrambler Therapy Technology (Model ST-5A) on December 23, 2020 (Product Code GZJ). Refer to the following websites for more information:

- https://www.accessdata.fda.gov/cdrh_docs/pdf8/K081255.pdf
- https://www.accessdata.fda.gov/cdrh_docs/pdf14/K142666.pdf
- https://www.accessdata.fda.gov/cdrh_docs/pdf20/K201458.pdf

(Accessed August 30, 2023)

Transcutaneous Electrical Nerve Stimulators

Transcutaneous electrical nerve stimulators (TENS) are regulated by the FDA as Class II devices. Products for TENS are too numerous to list. Refer to the following website for more information (use product codes GZJ, NUH, or NGX). Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed August 30, 2023)

Translingual Stimulation Devices

TLS devices are categorized as neuromuscular tongue stimulators to treat motor deficits. The Portable Neuromodulation Stimulator (PoNS) device was granted De Novo approval on March 25, 2021. The device is indicated for use as a short-term treatment of gait deficit due to mild to moderate symptoms from multiple sclerosis and is to be used as an adjunct to a supervised therapeutic exercise program in patients 22 years of age and over by prescription only. Refer to the following website for more information https://www.accessdata.fda.gov/cdrh_docs/pdf20/DEN200050.pdf.
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Policy History/Revision Information

Date	Summary of Changes
08/01/2024	**Coverage Rationale** • Updated language pertaining to medical necessity clinical coverage criteria for Neuromuscular Electrical Stimulation (NMES) and Functional Electrical Stimulation (FES); replaced reference to the "InterQual® Medicare: Post Acute & Durable Medical Equipment, Neuromuscular Electrical Stimulation (NMES)" with the "InterQual® Medicare: Post Acute & Durable Medical Equipment, Neuromuscular Electrical Stimulation (NMES) *NCD*" **Applicable Codes** • Added notation to indicate CPT/HCPCS codes 63650, 63655, 63685, A4438, A4593, A4594, E0762, E0764, and L8678 are not managed for medical necessity review for the state of Indiana at this time; refer to the most current *Prior Authorization and Notification List* for UnitedHealthcare Community Plan of Indiana • Removed notation indicating HCPCS codes E0770 and L8679 are not managed for medical necessity review for the State of Indiana at this time **Supporting Information** • Archived previous policy version CS036IN.08

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state, or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state, or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state, or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state, or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

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