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

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➲ 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.

Functional electrical stimulation (FES) is proven and medically necessary as a component of a comprehensive ambulation rehabilitation program in individuals with lower limb paralysis due to spinal cord injury (SCI) when all the following criteria are met:

- Demonstration of intact lower motor units (L1 and below) (both muscle and peripheral nerves)
- Muscle and joint stability for weight bearing at upper and lower extremities that can demonstrate balance and control to maintain an upright support posture independently
- Demonstration of brisk muscle contraction
- Demonstration of sensory perception sufficient for muscle contraction
- Demonstration of a high level of motivation, commitment, and cognitive ability for device use
- Ability to transfer independently
- Demonstration of independent standing tolerance for at least 3 minutes
- Demonstration of hand and finger function to manipulate controls
- Post-recovery from SCI and restorative surgery of at least 6 months
- Absence of hip and knee degenerative disease
- Absence of history of long bone fracture secondary to osteoporosis

FES is unproven and not medically necessary due to insufficient evidence of efficacy for treating any other indication not listed above.

Neuromuscular electrical stimulation (NMES) is proven and medically necessary for treating any of the following indications:

- Disuse muscle atrophy if:
  - The nerve supply to the muscle is intact; and
  - The disuse muscle atrophy is not of neurological origin but results from other conditions, for example casting, splinting, or contractures

  or
- When used as part of a comprehensive lower limb rehabilitation program following total knee arthroplasty; or
- To improve upper extremity function in persons with partial paralysis following stroke when used as part of a comprehensive rehabilitation program

NMES is unproven and not medically necessary due to insufficient evidence of efficacy for treating any condition not meeting the criteria above.

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 (TS) for gait rehabilitation

*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).

Medical Records Documentation Used for Reviews

Benefit coverage for health services is determined by the federal, state, or contractual requirements, and applicable laws that may require coverage for a specific service. Medical records documentation may be required to assess whether the member meets the clinical criteria for coverage but does not guarantee coverage of the services requested.

The patient's medical record must contain documentation that fully supports the medical necessity for the requested services. This documentation includes, but is not limited to, relevant medical history, physical examination, and results of pertinent diagnostic tests or procedures. Documentation supporting the medical necessity should be legible, maintained in the patient's medical record, and must be made available upon request.

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 federal, state, or contractual requirements 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

CPT Code	Description
*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
*A4543	Supplies for transcutaneous electrical nerve stimulator, for nerves in the auricular region, per month
*A4544	Electrode for external lower extremity nerve stimulator for restless legs syndrome
*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
*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
E0721	Transcutaneous electrical nerve stimulator, for nerves in the auricular region
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)
E0743	External lower extremity nerve stimulator for restless legs syndrome, each
E0744	Neuromuscular stimulator for scoliosis
E0745	Neuromuscular stimulator, electronic shock unit
*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

HCPCS Code	Description
*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.

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 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, 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 or placed 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 StimRouter Neuromodulation System, SPRINT PNS System, and the Freedom Peripheral Nerve Stimulator (PNS) (previously known as StimQ).

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). The ReActiv8 Implantable Neurostimulation System is an example of a restorative neurostimulation system.

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

Functional Electrical Stimulation (FES)

FES has been proposed for improving ambulation in individuals with gait disorders such as drop foot, hemiplegia due to stroke, cerebral injury, or incomplete SCI. Randomized controlled trials (RCTs) and case series for the use of FES in these other indications have primarily included small study populations with short-term follow-ups.

Nervous System Conditions

Spinal Cord Injury (SCI)

Hayes published an Evidence Analysis Research Brief (EARB) addressing home-based FES for rehabilitation following spinal cord injury (SCI) based on a review of six abstracts, including one RCT that was reported in three of the abstracts and one single-arm study that was reported in the other three abstracts. The brief stated that there was not enough published peer-reviewed literature to evaluate the evidence related to home-based FES for rehabilitation following SCI and that they did not find any clinical position statements or guidelines that addressed home-based FES for this indication, concluding that there was no/unclear support for its use in patients undergoing rehabilitation following SCI (2024).

Máté et al. (2023) conducted a systematic review and meta-analysis to examine the evidence for the potential of hybrid FES cycling to improve cardiorespiratory fitness for people with mobility disability related to a SCI. The systematic review included 13 published studies (10 uncontrolled acute exercise bout studies and three uncontrolled training studies) with six of the studies included in the meta-analyses. For 12 studies, the participants had SCI, with the time since injury ranging from two to 13.6 years. Some studies only included participants with a complete SCI, while other studies had a mixture of participants with complete and incomplete injuries. Most studies were considered to have fair methodological quality. There was a total of 119 participants included in the 13 studies (102 men and 17 women). The authors reported that hybrid FES cycling was moderately more effective than arm crank ergometry (ACE) in increasing peak volume of oxygen consumption ($\dot{V}$ o 2peak) from rest in the 10 studies (125 participants) that reported $\dot{V}$ o 2peak, and that there was a large effect on the increase of $\dot{V}$ o 2peak from rest for hybrid FES cycling compared with FES cycling in the five studies (36 participants) that reported on hybrid FES cycling compared with FES cycling. The authors also reported that longitudinal training with hybrid FES cycling showed a significant improvement in $\dot{V}$ o 2peak from pre to post intervention in the three studies (22 participants) that reported on aerobic fitness after hybrid FES cycling. Limitations of the study include the small sample sizes of the included studies, and the participants included in the subanalyses, the heterogeneity of the study designs and inclusion criteria among studies, and the publication bias and a lack of individual participant data as three of the studies appeared to have the same participant data for acute bouts of hybrid FES cycling and ACE (but was only included once in the meta-analysis). The authors concluded that hybrid FES cycling can improve cardiorespiratory fitness in people with SCI and that there is emerging evidence that hybrid FES cycling might increase aerobic fitness in people with mobility disability related to CNS disorders.

In a systematic review by Bekhet et al. (2022), the effect of using neuromuscular electrical stimulation (NMES) or FES, or both, on training on body composition parameters in individuals with SCI was evaluated. The review included 46 studies with a total sample size of 414 participants that evaluated NMES loading exercise and FES cycling exercise used in training. The authors reported that there was an average increase in muscle cross-sectional area of 26% (n = 33) and that 15 studies reported changes (both increase and decrease) in lean mass or fat-free mass with a range from -4% to 35%. Limitations noted included broad inclusion criteria for other interventions that made it difficult to determine the benefits that were due specifically to the electrical stimulation, the broad variability of NMES /FES parameters used across the studies, the small sample sizes, the variability of the levels of spinal cord injury included, the wide range of study designs (case reports, crossover, prospective and retrospective) with limited number of RCTs and the variability in durations and interventions. The authors concluded that the systematic review showed that the use of NMES/FES resulted in robust muscle hypertrophy and increase in lean mass and fat-free mass with inconclusive evidence about reduction in intramuscular mass. They recommended multi-center RCTs to consolidate previous research findings on body composition and to reach consensus about the most effective stimulation parameters needed to improve body composition in persons with SCI. The studies reviewed included the Griffin 2009 study previously summarized in this policy.

Sadowsky et al. (2013) conducted a single-center cohort study to examine the effect of long-term lower extremity FES cycling on the physical integrity and functional recovery in people with chronic SCI. Twenty-five individuals with chronic SCI (at least 16 months following injury) who received FES during cycling were matched by age, gender, injury level, severity, and duration of injury to 20 people with SCI who received range of motion (ROM) and stretching. The main outcome measure was change in neurological function, which comprised motor, sensory, and combined motor–sensory scores (CMSS) assessed by the American Spinal Injury Association Impairment scale. Response was defined as ≥ one point improvement. FES was associated with an 80% CMSS responder rate compared to 40% in controls. An average 9.6 CMSS point loss among controls was offset by an average 20-point gain among FES subjects. Quadriceps muscle mass was on average 36% higher and intra/inter-muscular fat 44% lower, in the FES group. Hamstring and quadriceps muscle strength was 30 and 35% greater, respectively, in the FES group. Quality of life (QOL) and daily function measures were significantly higher in FES group. The authors concluded that FES during cycling in chronic SCI may provide substantial physical integrity benefits, including enhanced neurological and functional performance, increased muscle size and force-generation potential, reduced spasticity, and improved QOL.

Harvey et al. (2010) conducted an RCT to determine the effectiveness of electrical stimulation (ES)-evoked muscle contractions superimposed on progressive resistance training (PRT) for increasing voluntary strength in the quadriceps muscles of people with SCI. A total of 20 individuals with established SCI (more than six months post injury) and neurologically induced weakness of the quadriceps muscles participated in the trial. Additional inclusion criteria were at least 90 degrees passive knee ROM and moderate neurologically induced weakness in their quadriceps muscles of one leg responsive to ES. Patients with a recent history of trauma to the lower extremity, currently participating in a lower limb strength or ES training program or limited ability to comply were excluded. Participants were randomized to experimental or control groups. The experimental group received ES superimposed on PRT to the quadriceps muscles of one leg three times weekly for eight weeks. The control group received no intervention. Assessments occurred at the beginning and at the end of the eight-week period. The four primary outcomes were voluntary strength [muscle torque in Newton meters (Nm)], endurance (fatigue ratio), and performance and satisfaction items of the Canadian Occupational Performance Measure (COPM; points). The between-group mean differences [95% confidence interval (CI)] for voluntary strength and endurance were 14 Nm (1 to 27; p = 0.034) and 0.1 (-0.1 to 0.3; p = 0.221), respectively. The between-group median differences (95% CI) for the performance and satisfaction items of the COPM were 1.7 points (-0.2 to 3.2; p = 0.103) and 1.4 points (-0.1 to 4.6; p = 0.058), respectively. The authors concluded the results provide initial support for the use of ES superimposed on PRT for increasing voluntary strength in the paretic quadriceps muscles of individuals with SCI however, there is uncertainty about whether the size of the treatment effect is clinically important. They also stated that it is not clear whether ES was the critical component of the training program or whether the same results could have been attained with PRT alone.

Additional evidence indicates that people with paraplegia can benefit from FES that exercises muscles without providing locomotion. In one study, electrically stimulated use of an exercise cycle by people with paraplegics restored muscle mass (Baldi, 1998). In another study, bone mineral density improved in some bones of patients with SCI after use of the FES bicycle (Chen, 2005). While most studies involved participants with many years of muscular atrophy, Baldi et al. utilized participants with less than four months of atrophy. Moreover, electrically stimulated isometric exercise stimulated bone remineralization that was not observed with electrically stimulated walking (Needham-Shropshire, 1997). Even if the ambulation provided by devices such as the Parastep significantly improves, it will still only be usable by a subset of patients with paraplegia such as those with T4-T11 SCIs (Klose, 1997). Stationary electrically stimulated exercise can be performed by a much larger group of patients including people with tetraplegia. To summarize, electrically stimulated ambulation cannot be considered safer or more beneficial than electrically stimulated stationary exercise unless the benefits of ambulation are shown to be superior in large-scale trials in which people with paraplegia are randomized to these two therapies. Further studies also need to be performed to confirm the benefits of electrically stimulated stationary exercise since the controlled trials conducted to date have used very small study populations and have assessed a limited set of outcome measures.

Cerebral Palsy (CP)

Moll et al. (2023) conducted a randomized cross-over trial was conducted with 25 children with unilateral spastic CP to study if FES of the peroneal nerve can improve body functions, activities, and participation, and could be an effective alternative treatment. Participants were aged four to 18 years (median age 9 years 8 months, 60% male) who were classified by the Gross Motor Function Classification System (GMFCS) as level I or II, with unilateral foot drop of central origin, and currently undergoing treatment with an AFO or adapted shoes. The study treatment sequence was randomized with each participant receiving 12 weeks of FES treatment (during which time each participant wore the WalkAide device) and 12 weeks of conventional treatment (AFO or adapted shoes), separated by a six-week washout period. Outcome measures included the Goal Attainment Scale (GAS), the Cerebral Palsy QOL questionnaire, and a three-dimensional gait analysis. The authors reported that 18 participants completed the trial and that the proportion of GAS goals achieved was not significantly higher in the FES versus the conventional treatment phase. According to the authors, there were no

changes found in the standard physical examination or regarding satisfaction with orthoses and feelings about the ability to dress themselves. The authors concluded that FES was not significantly worse than AFO; however, patient selection is critical, and a testing period and thorough follow-up are needed. Limitations of the study include the single center design, the high dropout rate, the short follow-up period, and the use of multiple physiotherapists performing the physical examinations.

In a prospective, open-label study on children with hemiplegic CP related foot drop who used dorsiflexion FES (DF-FES), Segal et al. (2023) assessed the effectiveness of the device over a five-month period of use. The study included 15 participants who were at least six years of age who attended all appointments and who showed good compliance. Each participant was assessed by motor function tests and the measurement of ankle biomechanical parameters at baseline, after one month and after five months. All testing was conducted by the same physiotherapist in the same order for all participants and at each visit. At baseline, tests were conducted while the child was wearing the DF-FES device (WalkAide) turned off and at one and five months, each test was carried out first with the device switched off and then with it switched on. There were 11 participants who dropped out between enrollment and the five-month mark, of which, eight (72%) withdrew due to a lack of a positive effect of FES on gait (as perceived by the participant and family), and three (28%) withdrew for unrelated reasons. The authors reported that improvement was noted at the one-month appointment although the difference between month one and month five was not significant. Falling frequency questionnaires filled out by the parents revealed a trend toward improvement in stability, although the results were not statistically significant. Limitations of the study include the single-center design, the small sample size, the low retention rate, and the lack of a control group. The authors concluded that the continuous use of DF-FES produced an early functional benefit and immediate therapeutic effect with better stability and postural control.

Zhu et al. (2022) conducted a meta-analysis to assess the effectiveness of FES devices in gait improvement in children with CP. Their analysis included nine studies with a total of 282 children with CP, of which, 140 children were in the FES treatment group and 140 children were in the control group. The authors reported that the data showed that the walking speed and step length were increased after FES compared to the control group. The authors noted that the randomization scheme and result report used in most studies were low risk although most studies had limitations in the blinding method of participants and subjects as most were single-blind studies. The authors concluded that FES could increase the walking speed and the walking step length which could improve the walking ability of children with CP. The authors recommended more research to support their findings.

In a parallel three-group, randomized, unblinded, single-center, cross-sectional study by Sansare et al. (2021), the effect of two training approaches, cycling with and without FES assistance, to that of a no-intervention control group on the cardiorespiratory fitness of children with CP was examined. The study included 39 participants between the ages of 10 and 18 years. They were randomized to one of the three study groups, FES (received FES-assisted cycle training, n = 15), VOL (underwent volitional cycling only, n = 11) or CON (received no treatment intervention, n = 13) with participant characteristics among the groups showing no significant differences in age, height, weight, and BMI among the three groups. Both treatment groups underwent a set-up / practice phase prior to baseline testing then were asked to cycle continuously for 30 minutes, three times a week for eight weeks at the target cycling power corresponding to 50–80% of their Karvonen-predicted target heart rate during the baseline incremental test. All participants were assessed for cardiorespiratory fitness at three time points: prior to training (PRE), at the end of eight weeks of training (POST), and during a washout period of eight weeks (WO). An additional assessment was performed midway through training to account for increased cardiorespiratory capacity and motor learning effects, and new HR and power targets were set. The average adherence to the training protocol in both the cycling groups was 91.9%, with no significant difference between the FES and VOL groups. The authors concluded that the study showed that, while FES-assisted cycling can enable children with CP to attain higher cycling cadences than cycling alone, or without any intervention, it did not show any significant improvements in peak VO2 (liters of oxygen per minute per kg body weight), and peak net HR [peak heart rate in beats per minute (bpm)]. They reported that the FES group made significant gains between PRE to POST and that all three study groups showed minimal changes between POST and WO which the authors stated is indicative of the ability to maintain the gains made during training.

Moll et al. (2017) conducted a systematic review to assess the effect of functional electrical stimulation (FES) of ankle dorsiflexors in children and adolescents with spastic CP during walking. A search, using predetermined terms, was conducted using PubMed/MEDLINE, Embase, the Physiotherapy Evidence Database (PEDro), Web of Science, CINAHL, and the Cochrane Library. Outcomes were reported according to the International Classification of Functioning, Disability and Health (ICF). The ICF domains are classified by body, individual and societal perspectives by means of two lists: a list of structure and function and a list of domains of participation and activity. A total of 780 articles were identified and after review, 14 articles were included, including two small randomized controlled trials. In total, 127 participants received FES of the ankle dorsiflexors (14 bilaterally affected and 113 unilaterally affected). The participants' ages ranged from five to 19 years and the Gross Motor Function Classification System (GMFCS) level ranged from I to III. The authors concluded

that: At the ICF participation and activity level, there is limited evidence for a decrease in self-reported frequency of toe-drag and falls; At the ICF body structure and function level, there is clear evidence (level I to III studies) that FES increased (active) ankle dorsiflexion angle, strength, and improved selective motor control, balance, and gait kinematics, but decreased walking speed. Adverse events included skin irritation and acceptance issues. The authors further stated that it cannot be concluded that FES (of the ankle dorsiflexors) improves functioning at the activity and participation level however, current evidence supports the potential role of FES as an alternative to classic orthotic treatment. The authors recommend that future studies should focus on the domain of activity and participation. The findings are limited by the study design of most of the included studies.

A 2016 RCT by El-Shamy and Abdelaal was conducted to investigate the effects of the WalkAide FES on gait pattern and energy expenditure in children with hemiplegic CP. Seventeen children were assigned to the study group, whose participants received FES (pulse width, 300 μs; frequency, 33 Hz, 2 hours/d, three days per week for three consecutive months). Seventeen other children were assigned to the control group, whose participants underwent a conventional physical therapy exercise program for three successive months. Baseline and post-treatment assessments were performed using the GAITRite system to evaluate gait parameters and using an open-circuit indirect calorimeter to evaluate energy expenditure. Children in the study group showed a significant improvement when compared with those in the control group ($p < 0.005$). The gait parameters (stride length, cadence, speed, cycle time, and stance phase percentage) after treatment were (0.74 m,119 steps/min, 0.75 m/s, 0.65 s, 55.9%) and (0.5 m,125 steps/min, 0.6 m/s, 0.49 s, 50.4%) for the study group and control group, respectively. The mean energy expenditures after treatment were 8.18 ±0.88 and 9.16 ±0.65 mL/kg per minute for the study and control groups, respectively. The authors concluded that WalkAide FES may be a useful tool for improving gait pattern and energy expenditure in children with hemiplegic CP. The study was limited to a small sample size.

Cerebrovascular Accident (CVA)

Galvão et al. (2024) conducted a systematic review and meta-analysis to analyze the efficacy and effectiveness of cycling using FES, either combined with exercise programs or alone, to improve strength, balance, trunk control, walking speed, walking distance and ADLs in individuals in early subacute CVA recovery. The study included five RCTs with 187 participants (age range 56 to 74 years) who were within 16 and 60 days of post-stroke recovery. The authors reported that cycling using FES combined with exercise programs promoted relevant benefits in trunk control and walking distance and that cycling using FES alone compared to exercise programs promoted similar benefits in strength, balance, walking speed, walking distance, and ADLs. Limitations of the study include the heterogeneity in the parameters used in the studies and in the FES, systems used, the limited number of studies available for inclusion, and the lack of standardization in the motor impairment definition of the participants included in the studies. The authors concluded that their systematic review provided low-to-moderate-quality evidence that cycling using FES may be an effective strategy to consider in improving motor function and activity outcomes for individuals in the early subacute phase of CVA recovery.

Matsumoto et al. (2023) conducted a multi-center, randomized, controlled, open-label trial with 203 adult Japanese participants, aged 25 to 85 years who had experienced an initial stroke within six months of the study and had post-stroke sequelae including hemiplegic gait disorder (foot drop). The participants were divided into a treatment arm who received FES (n = 102) and a control group (n = 101), of which, 84 participants in the FES group and 85 participants in the control group completed the study. The data of the primary outcome of 184 participants (92 in each group) were analyzed after excluding 19 participants who did not receive any intervention or whose data were not available. The participants in the FES group underwent a 40 min training program five days a week for eight weeks receiving FES via the Walkaide® device while participants in the control group received a 40-minute training program without FES five days a week for eight weeks. The authors reported that FES did not significantly improve the distance covered by post-stroke participants with foot drop in the barefoot 6-minute walk test (6MWT) and that there were no group differences in walking speed, cadence, or in the functional ambulation classification grade in the FES group but that there was a tendency toward improved receptivity to gait. The authors concluded that the use of FES did not show efficacy in the treatment of Japanese convalescent stroke patients with foot drop.

Sannyasi et al. (2022) conducted a single-center, prospective, cross-over study to compare the gait parameters in patients with footdrop following stroke for at least three months using an ankle-foot orthosis (AFO) and FES. The study included 20 participants (19 males and one female) who had hemiplegia following a cerebrovascular accident (CVA). The participants were divided into two groups of ten each (group A and group B) and were observed to see if the order of use for AFO and FES had any effect on the outcome. All participants received two hours of gait training every day for two weeks in addition to their regular physical and occupational therapy. The participants in group A received gait training with AFO for the first week followed by FES using the WalkAide device during the second week while group B received gait training with FES using the WalkAide in the first week and AFO during the second week. Patient satisfaction, primary and secondary outcome measures were gathered on day one and at the end of each week after training with the AFO or FES device. The authors reported that statistically significant improvement in gait speed and walking endurance was seen with

both AFO and FES compared to baseline and that there was a statistically significant improvement between the groups in favor of FES for gait speed and walking endurance. The authors also reported that there was a statistically significant improvement in time to complete the TUG test (the time it takes to get up from a chair, walk three meters and return to sit on the chair) among users of FES compared to AFO and that FES exhibited statistically significant improvement in stance-swing ratio and single limb support on paretic limb as compared to AFO. The order of trial did not show any effect on outcome measures between groups except for the 6MWT. Limitations of the study include the single center design, the short duration of FES intervention and the high predominance of males vs. females in the study. The authors concluded that the study showed that both AFO and FES had significant improvement in gait parameters compared to barefoot walking and that FES users demonstrated statistically significant improvement in walking speed and endurance compared to AFO users. The authors recommended further trials to evaluate the long-term therapeutic benefits, carry-over effects and cost-effectiveness of FES devices for management of footdrop.

In their Health Technology Assessment (HTA) on the effectiveness of rehabilitative FES for foot drop in patients during the acute or subacute phases of stroke recovery, Hayes (2022a, updated 2024) reviewed 10 studies including nine RCTs and one crossover RCT. The studies varied in their evaluation of FES relative to no placebo or placebo FES, the use of an ankle-foot orthosis (AFO), and adjunct use of electromechanical gait training (EMGT) and neuromuscular electrical stimulation (NMES). The update for 2024 found two newly published RCTs; however, their ratings and conclusions remained unchanged. The HTA stated that there was an overall low-quality body of evidence due to study limitations (including small sample sizes, attrition, lack of power analysis or blinding, and short-term follow-up), the use of different FES devices among the studies, the variation in treatment intensity among the studies, the limited number of studies for the different comparators, inconsistencies in the evidence of benefit and insufficient follow up to assess long-term durability of the benefit of FES. The report concluded that, while FES treatment appears relatively safe, there was particular concern across the studies regarding the lack of consistent evidence that FES improved measures of functional recovery and QOL. They recommended additional RCTs with better standardization of FES devices and treatment protocols with longer follow-up to establish whether FES improves outcomes related to conservative therapies for foot drop due to stroke that occurs less than one year prior to starting treatment with FES.

Hayes (2022b, updated 2024) also published an HTA on the effectiveness of FES for foot drop in the chronic phase of stroke recovery that identified eight RCTs and one crossover RCT which evaluated FES for treatment of foot drop in patients who had experienced a CVA one year or more before starting FES. In the most recent update, Hayes has not identified any newly published studies since their 2022 report, so their recommendations remain unchanged. The report stated that the body of evidence for assistive FES with skin-surface electrodes and for rehabilitative FES with skin-surface electrodes were both low in quality while the body of evidence for assistive FES with implanted electrodes was very low in quality. The studies in the HTA were downgraded to fair quality due to limitations in the study designs (small size, dropout rate), incomplete statistical analysis, lack of complication reporting, lack of blinding or blind analysis of data, low intensity or short duration of FES treatment and/or short follow up periods. The HTA concluded that FES with skin-surface electrodes did not provide any statistically significant improvements in walking, stroke recovery or quality-of-life measures when compared to ankle-foot-orthoses. However, when assistive use of FES with skin-surface electrodes was compared to conservative therapies that included AFOs or to no FES in patients undergoing physical therapy for gait disorders, the evidence showed limited improvements. The report recommended additional RCTs to demonstrate the benefit of assistive use of FES relative to AFOs and to the benefit of rehabilitative use of FES to ascertain the reliability and durability of benefits that may diminish long-term once FES is discontinued.

A Clinical Evidence Assessment (CEA) published by ECRI (2022) on the safety and effectiveness of FES for physical rehabilitation in patients with hand paralysis found that functional neuromuscular stimulation (FNMS) improved hand function when used to supplement rehabilitation in patients with chronic paresis due to stroke but not in patients with acute or subacute paresis. The CEA included a systematic review with meta-analysis of 26 RCTs (including the Jonsdottir 2017 study below) and review of an additional seven RCTs that were of high risk of bias from small sample sizes and single-center focus. The authors indicated that the meta-analysis reported pooled outcomes with sufficient precision to support conclusions; however, study heterogeneity was significant, limiting generalizability of the findings to specific patient populations. They noted that most of the studies in the systematic review and the additional studies involved prototype or research devices so the findings may not fully generalize to patients treated with commercial devices in clinical practice.

Loh et al. (2022) completed a meta-analysis of six RCTs published between 2012 and 2020 to evaluate the effectiveness of contralaterally controlled functional electrical stimulation (CCFES) compared to NMES on upper extremity motor recovery in post-stroke patients. The studies included a combined 267 participants (137 in the CCFES treatment group and 130 in the cyclic NMES group) during various phases of post-stroke recovery with one that investigated acute phase stroke, one studied chronic phase stroke, three evaluated subacute phase stroke and one that studied both subacute and chronic phase stroke. The participants in both intervention groups in all of the RCTs received treatment and background

interventions for the same length of time. The risk of bias assessment indicated that four studies were identified as low risk, one as having some concerns, and one was identified as high risk. The authors stated that the results of their meta-analysis showed that the CCFES group demonstrated greater improvement than the NMES group in Upper Extremity Fugl-Meyer Assessment scores (included in all studies), the Box and Block test (included in three studies), the active ROM measurements (included in four studies) and the modified Barthel Index (included in two studies); however, results for the Arm Motor Abilities Test (included in three studies) did not differ significantly between stimulation types. Limitations noted by the authors included the lack of blinding in all of the studies, the small number of RCTs included (of which, half of them originated from the same authors), the variability of the phase of stroke recovery or severity of impairment at baseline, and that all of the comparison groups included only NMES. The authors concluded that CCFES might be an alternative form of intervention for post stroke treatment that may facilitate upper extremity motor function recover. They recommend more RCTs to verify the efficacy and effects of CCFES and to compare CCFES with other modalities or interventions.

Hayes published an HTA that provided a Comparative Effectiveness Review on the use of FES in addition to conventional occupational and physical therapy (COPT) compared with COPT alone for upper extremity (UE) rehabilitation post stroke. The review included 10 RCTs (including the Jonsdottir 2017 study below) and found that the addition of FES to COPT is at least as effective as COPT alone for improving some outcomes in post-stroke patients undergoing UE rehabilitation with some studies showing improvement in activities of daily living (ADLs), motor function and shoulder subluxation. The results were mixed, and the overall body of evidence was of low-quality and there was a lack of clarity regarding clinically meaningful changes. The report also noted that the efficacy of FES with COPT is similar to COPT alone regarding spasticity outcomes. The report concluded that additional information is needed to determine whether FES effectiveness varies by the type, location, or chronicity of the stroke, that long-term (> 18 months) efficacy is needed, and that optimal parameters for FES treatment have yet to be established (2021, updated 2022).

A systematic review and meta-analysis by Jaqueline da Cunha et al. (2021) evaluated the effectiveness of FES applied to the paretic peroneal nerve and its influence on gait speed, active ankle dorsiflexion mobility, balance, and functional mobility. Electronic databases were searched for RCTs or crossover trials that focused on the effectiveness of FES with or without other therapies on individuals with foot drop after stroke. The review included 14 studies that provided data for 1115 participants who had sustained a stroke between less than one month and 108 months prior to their study participation. The study demonstrated that FES alone did not enhance gait speed when compared to conventional treatments although when FES was combined with supervised exercises, gait speed was better than supervised exercises alone. It also showed that FES had no effect when combined with unsupervised exercises on gait speed and that the data was inconclusive when FES was combined with regular activities at home. When FES was compared with conventional treatments, the analysis determined that it improved ankle dorsiflexion, balance, and functional mobility. The authors concluded that the meta-analysis showed the quality of evidence was low for positive effects of FES on gait speed when combined with physical therapy and that FES can improve ankle dorsiflexion, balance, and functional mobility. They stated that the results of the systematic review and meta-analysis should be interpreted carefully considering the low quality of evidence and high heterogeneity of the data.

ECRI published a Clinical Evidence Assessment on the MyndMove FES device that has been developed to voluntary hand and arm movement in patients with paralysis after a stroke or spinal cord injury. The focus of the ECRI report, however, was on the device's safety and efficacy in adults post-stroke. The report determined that the evidence is inconclusive due to limited available published evidence that included two very small single center, unblinded RCTs and one pre-post study. ECRI concluded that the studies are too high risk of bias to be conclusive and that larger, multicenter RCTs are needed to demonstrate improvement in pain, spasticity, or QOL and to demonstrate that the benefits of the device are sustainable after therapy completion (2020).

Nascimento et al. (2020) conducted a systematic review and meta-analysis to evaluate the efficacy of ankle-foot orthoses (AFOs) and FES to the pre-tibialis muscle applied throughout the day to reduce footdrop after stroke. The review included 11 parallel RCTs that assessed the use of AFOs and FES on walking speed and balance in ambulatory adults who were moderately disabled following their stroke. The RCTs included 1135 participants between 47 and 65 years of age who were in both acute and chronic phases of recovery. The authors reported that AFO with FES significantly increased walking speed, compared with no intervention/placebo; however, the results regarding the efficacy of AFO with FES on balance were inconclusive. The meta-analysis also found that AFOs alone were not superior to FES for improving walking speed or balance after stroke. The authors concluded that the systematic review provided moderate-quality evidence that both AFOs and FES improve walking speed after stroke, but the effects on balance remain unclear. The limitations of the review identified by the authors include lack of blinding of the therapists, participants, and assessors, lack of description of whether an intention-to-treat analysis was done, the small number of included studies and the number of participants per group varied across trials. There was also a lack of evaluation of the maintenance of effects beyond the intervention

period. The authors recommend future RCTs investigate the effects on clinical outcomes related to social participation and adverse events in people with stroke.

A systematic and meta-analysis by Eraifej et al. aimed to evaluate the effectiveness of post-stroke upper limb FES on ADL and motor outcomes. Systematic review of randomized controlled trials from MEDLINE, PsychINFO, EMBASE, CENTRAL, ISRCTN, ICTRP and ClinicalTrials.gov. Twenty studies met inclusion criteria. Outcomes were ADL (primary), functional motor ability (secondary) and other motor outcomes (tertiary). Quality assessment was determined using GRADE (Grading of Recommendations Assessment, Development and Evaluation) criteria. In 6 studies, no significant benefit of FES was found for objective ADL measures (FES group participants = 67). A significant benefit on ADLs was demonstrated in an analysis of three studies where FES was initiated on average within two months post-stroke (n = 32). No significant ADL improvements were seen in three studies where FES was initiated more than one year after stroke (n = 35). Quality assessment using GRADE found very low-quality evidence in all analyses due to heterogeneity, low participant numbers and lack of blinding. Meta-analyses gave rise to certain limitations. including but not limited to the utilization of many different measurement instruments and only a minority were employed by more than a few studies, as well as inadequate participant blinding in most studies. The authors concluded that FES is a promising therapy which could play a part in future stroke rehabilitation. There is a need for high quality large-scale randomized controlled trials of upper limb FES after stroke to draw firm conclusions regarding its efficacy or its optimum therapeutic window (2017).

Jonsdottir et al. (2017) conducted a RCT assessing the efficacy of myoelectric continuous control FES (MeCFES) when used as a part of task-oriented therapy (TOT) in persons who are post-stroke. Eighty-two acute and chronic stroke victims were recruited and randomized to receive either the experimental MeCFES assisted TOT (M-TOT) or conventional rehabilitation care including TOT (C-TOT). Both groups received 45 minutes of rehabilitation over 25 sessions. Outcomes were Action Research Arm Test (ARAT), Upper Extremity Fugl-Meyer Assessment (FMA-UE) scores and Disability of the Arm Shoulder and Hand questionnaire. Sixty-eight individuals completed the protocol, and 45 were seen at follow up five weeks later. There were significant improvements in both groups on ARAT (median improvement: MeCFES TOT group 3.0; C-TOT group 2.0) and FMA-UE (median improvement: M-TOT 4.5; C-TOT 3.5). Considering subacute subjects (time since stroke less than six months), there was a trend for a larger proportion of improved participants in the M-TOT group following rehabilitation (57.9%) than in the C-TOT group (33.2%). This is the first large multicenter RCT to compare MeCFES assisted TOT with conventional care TOT for the UE. No AEs or negative outcomes were encountered. The authors concluded that MeCFES can be a safe adjunct to rehabilitation and could promote recovery of upper limb function in persons after stroke, particularly when applied in the subacute phase. Several study limitations were identified for example, the predicted sample size needed to make a definitive conclusion as to the efficacy of the MeCFES was not reached, there may have been differences in use of the device between centers, and missing data where 14 of 82 enrolled participants failing to provide follow-up data and of those nine had a baseline assessment. Additional studies are still needed to clarify the utility of meCFES for patients who experience a stroke.

In this study, de Sousa et al. (2016) conducted a blinded, multi-institutional, RCT to determine whether active FES cycling as a supplement to standard care would improve mobility and strength more than standard care alone in individuals with a sub-acute acquired brain injury caused by stroke or trauma. The control group (n = 20) received standard care, which consisted of a minimum of one-on-one therapy with a physiotherapist at least one hour per day. In addition, participants could join group exercise classes or have another hour of one-on-one therapy, if available. The study group (n = 20) received an incremental progressive, individualized FES cycling program five times a week for four weeks, along with standard therapy. The primary outcomes measured were mobility and strength of the knee extensors of the affected lower limb. The secondary outcomes were strength of key muscles of the affected lower limb, strength of the knee extensors of the unaffected lower limb, and spasticity of the affected plantar flexors. On admission to the study, most participants could not walk or required a high level of assistance to walk/transfer. Only two individuals could ambulate without assistance at the end of four weeks. The mean composite score for affected lower limb strength was seven out of 20 points, reflecting severe weakness. The authors concluded that four weeks of FES cycling in addition to standard therapy does not improve mobility in people with a sub-acute acquired brain injury. Further studies could clarify the effects of FES cycling on strength, although the clinical significance may be limited without its accompanying impact on mobility.

Multiple Sclerosis (MS)

Máté et al. (2024) conducted a pilot study to investigate the cardiorespiratory, power, and participant-reported perceptions during acute bouts of FES cycling, voluntary cycling, and FES cycling combined with voluntary cycling (FES assist cycling). The study included ten people (nine female, 52.4 ±9.9 years) with severe MS who undertook three exercise trials on a leg cycle ergometer with Trial 1 including 30 minutes of FES cycling, Trial 2 including two 10-minute bouts of voluntary cycling separated by 10 minutes of rest, and Trial 3 including a combination of Trial 1 and Trial 2. Outcome measures included volume of oxygen consumption (VO_2), cycle power output, heart rate, rate of perceived exertion (RPE), and post-exercise perceptions of pain and fatigue. The authors reported that the average VO_2 during the 30-minute trials was significantly higher for FES assist cycling compared to voluntary cycling with a large effect size. The

authors also reported that participants had similar RPE at the end of FES cycling, voluntary cycling, and FES assist cycling while self-reported pain was higher during both FES cycling and FES assist cycling than voluntary cycling, both with large effect sizes, although there was no difference in self-reported fatigue at the end of each trial. The authors concluded that the study found FES assist cycling produced significantly higher VO_2 values than voluntary cycling, although the clinical significance of the differences was unknown. Limitations of the study included the small sample size, the inclusion of only one male, the lack of randomization of the order of trials, and the lack of regression analysis between disability levels.

Hayes (2021, updated 2023) published an HTA focusing on the use of FES for treatment of foot drop in patients with MS. In the eight studies reviewed, the goals were to improve gait, walking speed, QOL and overall functional mobility. The studies consisted of three RCTs, two randomized crossover trials, two case-control studies and one pretest-posttest study. Six of the studies used the Odstock FES device and three studies used the WalkAide FES device. The 2023 update stated that no newly published studies were found. The assessment stated that FES poses little risk of serious adverse events because it is noninvasive and involves low levels of electrical stimulation. Minor complications included pain, muscle spasms, weakness and pain, temporary paresthesia, light-headedness, increased falls, skin irritation and knee hyperextension. The authors noted that the body of evidence for FES and its efficacy to treat foot drop in patients with MS was low in quality due to the individual study limitations, use of different FES devices and limited number of studies for comparisons. The studies individually were found to be of low quality due to small size, observational design, high dropout rates, incomplete statistical analysis, potential bias from previous experience with the therapy being evaluated and short follow-up times. The report concluded that a low-quality body of evidence shows FES improves walking speed and duration with reduced exertion at about the same benefit level as AFOs and that FES improves psychological outcomes and perceived but not actual exertion. The authors recommend additional RCTs of FES versus AFOs to validate the psychological and perceived exertion benefits and to determine the durability of benefits over time.

In a systematic review investigating the effect of FES used for foot drop on health-related quality of life (HRQOL) in adults with MS, Miller et al. (2019) evaluated the results of eight studies that included one RCT, one randomized crossover trial, three experimental nonrandomized studies, and three observational studies. The total number of participants was 168 with 63% female and the sample sizes in the study groups varied from two to 64. Participants in these studies were older than 18 years, had a diagnosis of MS, presented with foot drop (unilateral or bilateral), and had used FES. Selected studies required at least one validated HRQOL outcome measure that assessed the effect of FES to be reported. The authors found that seven of the studies demonstrated significant positive effects of FES on different aspects of HRQOL as measured by the 29-item Multiple Sclerosis Impact Scale, 36-item Short Form Health Status Survey, Canadian Occupational Performance Measure, and Psychosocial Impact of Assistive Devices Scale. The authors concluded that the review showed that FES had a positive effect on aspects of HRQOL in people with MS; however, the variety of HRQOL outcomes used made it difficult to determine definitive conclusions. Future larger-scale RCTs with long-term follow-up are recommended to better understand the effect of FES on HRQOL. Limitations that the authors noted include the small number of studies, small number of participants, lack of control comparators and the broad variety of HRQOL outcomes used in the studies made it difficult to determine definitive conclusions from this review. They recommend further qualitative studies to understand how FES affects HRQOL, before the most appropriate HRQOL measures can be identified to determine the effectiveness of FES on HRQOL in people with MS and that future high-quality research should aim to capture the effect of FES on clinically meaningful aspects of HRQOL in longer-term studies.

Broekmans et al. (2011) conducted an RCT involving 36 persons with MS to examine the effect(s) of unilateral long-term (20 weeks) standardized resistance training with and without simultaneous ES on leg muscle strength and overall functional mobility. The authors found that long-term light to moderately intense resistance training improves muscle strength in persons with MS, but simultaneous ES does not further improve training outcome.

Circulatory System Conditions

Zeng et al. (2024) conducted a systematic review and meta-analysis of RCTs to compare the efficacy of FES versus conventional exercise training or placebo in patients with chronic heart failure (CHF). The study included 18 RCTs (including the Kadoglou 2017 study below) that compared the effects of FES and control treatment on participants with CHF that were included in both qualitative and quantitative analyses. Six of the studies were based on comparing FES with cycle (including aerobic exercise, cycling training, etc.), and 10 studies that were based on comparing FES with control (including normal care and sham FES). A total of 777 adult, predominantly male, participants with CHF were included in the studies. The authors reported that FES significantly improved peak oxygen consumption, increased six-minute walking distance, and improved QOL when compared to control but that traditional exercise rehabilitation therapy was more successful than FES in improving peak oxygen consumption, six-minute walking distance and QOL. The subgroup analysis completed by the authors showed that outcomes significantly improved under FES for both participants with CHF with reduced ejection fraction and participants with CHF with preserved ejection fraction, but that the difference was insignificant between groups of aerobic exercise and FES on participants with CHF with reduced ejection fraction.

Limitations of the study include the small study populations and short follow-up periods of the included RCTs, the heterogeneity of the study designs, and the lack of data and inclusion of patients with higher NYHA classifications. The authors concluded that the study demonstrated that FES improved cardiopulmonary function and QOL in participants with CHF and that participants with CHF with reduced ejection fraction benefited more from FES than participants with CHF with preserved ejection fraction.

In a systematic review and meta-analysis of 14 RCTs, Wang et al. (2022a) evaluated the effectiveness of FES of the legs in 518 study participants with heart failure. The authors stated that the pooled estimates demonstrated that FES significantly improved peak oxygen consumption (measure included in eight of the reviewed RCTs, n = 321), the 6MWT(10 RCTs, n = 380) and in the Minnesota Living with Heart Failure Questionnaire QOL score (nine RCTs, n = 383) while muscle strength of the lower extremities was not significantly improved in the FES treatment group compared with the control group (five RCTs, n = 218). They also stated that subgroup analysis showed that FES significantly improved peak oxygen consumption, 6MWT and Minnesota Living with Heart Failure Questionnaire QOL score in the heart failure with reduced ejection fraction and the heart failure with preserved ejection fraction subgroups. The authors assessed the quality of the RCTs as “fair” for six of the studies and “good” for the other eight studies. The conclusion reached by the authors was that FES can effectively improve cardiopulmonary function and QOL in patients with heart failure but does not significantly improve muscle strength in legs. Limitations acknowledged by the authors included that most of the included studies had potential bias risks, which limited the strength of the results, the limited availability of studies for inclusion, the heterogeneity of the studies, the FES treatments and muscles stimulated, and that seven of the RCTs used sham FES with sensory input or low-intensity stimulation of the control group which might have influenced outcomes.

Kadoglou et al. (2017) performed a randomized, placebo-controlled study to investigate the effects of FES on the lower limbs as an alternative method of training in patients with CHF. Participants deemed stable (n = 120) (defined by New York Heart Association (NYHA) class II/III and mean left ventricular ejection fraction (LVEF) of 28 ±5%), were randomly selected for either a six-week FES training program or placebo. Participants were followed for up to 19 months for death and/or hospitalization due to HF decompensation. At baseline, there were no significant differences in demographic parameters, HF severity, or medications between groups. During a median follow-up of 383 days, 14 participants died (11 cardiac, three non-cardiac deaths), while 40 participants were hospitalized for HF decompensation. Mortality did not differ between groups, although the HF-related hospitalization rate was significantly lower in the FES group. The latter difference remained significant after adjustment for prognostic factors: age, gender, baseline NYHA class and LVEF. Compared to placebo, FES training was associated with a lower occurrence of the composite endpoint (death or HF-related hospitalization) after adjustment for the above-mentioned prognostic factors. The authors concluded that six weeks of FES training in individuals with chronic HF reduced the risk of HF-related hospitalizations without affecting the mortality rate. The beneficial long-term effects of this alternative method of training require further investigation.

Miscellaneous Conditions

In a prospective, assessor-blinded RCT evaluating FES-assisted cycle therapy for mechanically ventilated adults in an intensive care unit (ICU), Waldauf et al. (2021) randomized 150 participants to either receive functional electrical stimulation-assisted cycle ergometry (FESCE) or standard therapy. The first rehabilitation occurred 63 versus 68 hours after ICU admission in the intervention versus control groups, respectively. Follow-up through six months was completed for 42 (56%) of the participants in the intervention group and 46 (61%) of participants in the control group. The authors reported that FESCE did not improve physical disability six months after surviving critical illness for mechanically ventilated participants with anticipated long ICU stays. They noted that, at ICU discharge, there were no differences in the ICU length of stay or functional performance. The authors stated that limitations to their study included a higher-than-expected mortality (41% were not alive at six months), the single-center design and their standard protocol for intensive rehabilitation therapy in the control group. The authors recommended future trials emphasize progressive mobility elements in the interventional group, enroll more homogeneous patient populations and involve patients in multiple centers.

Fossat et al. (2018) investigated whether early in-bed leg cycling plus ES of the quadriceps muscles added to standardized early rehabilitation would result in greater muscle strength at discharge from the ICU in a single center blinded RCT enrolling 314 critically ill adults. Participants were randomized to early in-bed leg cycling plus ES of the quadriceps muscles added to standardized early rehabilitation (n = 159) or standardized early rehabilitation alone (usual care, n = 155). The primary outcome was muscle strength at discharge from the ICU assessed by physiotherapists blinded to treatment group using the Medical Research Council grading system (score range, zero to 60 points; a higher score reflects better muscle strength). Functional autonomy and health related QOL were assessed at six months. Of the 314 participants, 312 completed the study and were included in the analysis. The median global Medical Research Council score at ICU discharge was higher in the usual care group than in the intervention group, scoring 51 and 48, respectively. There were no significant differences between the groups at six months. The authors concluded that adding

early in-bed leg cycling exercises and ES of the quadriceps muscles to a standardized early rehabilitation program did not improve global muscle strength at discharge from the ICU.

Clinical Practice Guidelines

National Institute for Health and Care Excellence (NICE)

In the NICE guideline regarding rehabilitation after traumatic injury, NICE states that, for rehabilitation after spinal cord injury, additional techniques and specialized equipment (such as FES, gait orthoses, bodyweight-supported gait training and robotic devices) should be considered to promote mobility, upper limb function and independent walking (2022).

Neuromuscular Electrical Stimulation (NMES) for Muscle Rehabilitation

Although the evidence is limited, NMES for the treatment of disuse atrophy in individuals where the nerve supply to the muscle is intact is supported by evidence. There is some evidence that the use of NMES may be an effective rehabilitative regimen for swallowing disorders or to prevent muscle atrophy associated with intensive care unit acquired weakness and prolonged knee immobilization following ligament reconstruction surgery or injury; however, controlled clinical trials are necessary to determine if the addition of NMES to the current standard rehabilitation programs will improve health outcomes.

Musculoskeletal System Conditions

Zhao et al. (2022) conducted an RCT to evaluate the feasibility of using NMES for enhanced recovery after total hip replacement (THR). The single center, open label study included 60 participants who were randomized into a treatment group (n = 30; 12 males, age 53.1 ±5.7 years) who received NMES via the geko™ device and a control group (n = 30, 9 males, age 53.4 ±5.5 years) who did not receive NMES following their THR by the same surgeon. The NMES group participants were required to wear the NMES device for a minimum of 30 minutes each session, added up to 20 sessions over five days. Data were collected prior to surgery (Day 0), and post-operative days one, three and five. The authors reported that there was a significant difference between the two groups with respect to pain on postoperative days one and three during mobilization but that there was no significant difference between the two groups regarding pain values on postoperative day five. The authors also reported that there was no significant difference in the mean swelling measured of the calf or thigh circumference before THR surgery but that the between-group differences in mean change of calf circumference were significant on postoperative days three and five while the postoperative change in thigh circumference in the two groups showed very little significance on any of the postoperative days. Limitations of the study include the short follow-up period, the open label, single-center design, and the small sample size. The authors concluded that the results of the study suggested that NMES is partly useful for enhanced recovery after THR surgery, and they recommended a larger study be conducted to determine its effectiveness on compelling data. The visual analog scale (VAS) pain score was used to quantify postoperative pain while moving on postoperative days one, three and five, and lower limb swelling was examined in the supine position by taking measures of the circumference of both the thigh (10 cm above the patella) and the calf (10 cm below the tibial tubercle) at baseline and on postoperative days one, three and five.

In a prospective, single-blind, single center RCT that investigated the role of NMES in increasing femoral venous blood flow after total hip replacement surgery and that evaluated the potential effects of NMES on preventing postoperative deep vein thrombosis (DVT), Calbiyik and Yilmaz (2022) concluded that there was a significant increase in femoral vein peak velocity (VPV) in the study group that received NMES which may indicate a potential effect of NMES in preventing postoperative DVT. Their study included 64 participants over 60 years old that were randomly divided into two groups with one group receiving NMES and low -molecular-weight heparin (n = 32) and the second group (n = 32) receiving a low-molecular-weight heparin plus a compression bandage. All participants had the same surgeon, same surgical approach (modified Gibson incision) and were operated on in the same position (lateral Sim's position). The length of hospital stay and the frequency of leg edema before and after surgery were similar in both groups. The authors reported that there was no difference between the groups in terms of the presence of preoperative and postoperative leg edema but that the calf diameter was significantly lower in the NMES group than in the non-NMES group in both the preoperative and postoperative period. The authors also reported that the femoral VPV was similar between the two groups in the preoperative period but was significantly higher in the NMES group than in the non-NMES group postoperatively. They reported that the femoral VPV after total hip prosthesis increased more in the NMES group (43.2%) compared with the non-NMES group (16.3%). The D-dimer value in the preoperative period was reported to be lower than on postoperative days one and five in the non-NMES group while in the NMES group, a statistically significant difference was found between the preoperative and postoperative test results as the D-dimer values were significantly lower on the fifth postoperative day than on the first postoperative day, and the preoperative value was significantly lower than the fifth postoperative day value. The authors recommended further research to evaluate the potential of NMES to prevent DVT in combination with other thromboprophylaxis modalities and to evaluate optimal parameters of NMES and stimulation location.

Wellauer et al. (2022) conducted a randomized controlled trial (RCT) to compare the effectiveness of a home-based neuromuscular electrical stimulation (NMES) program applied to the quadriceps of the nonoperative side against sham-NMES as a complement to standard rehabilitation on knee extensor neuromuscular function in patients following anterior cruciate ligament (ACL) reconstruction. Twenty-four participants completed the six-week NMES (n = 12) or sham-NMES (n = 12) post-operative interventions and were tested at different time points for neuromuscular function and self-reported knee function. Isometric, concentric, and eccentric strength deficits (muscle weakness) increased from pre-surgery to 24 weeks post-surgery in the sham-NMES group ($p < 0.05$), while no changes were observed in the NMES group. On the stimulated (nonoperative) side, quadriceps voluntary activation and muscle thickness were respectively maintained ($p > 0.05$) and increased ($p < 0.001$) as a result of the NMES intervention, contrary to sham-NMES. Self-reported knee function improved progressively during the post-operative phase ($p < 0.05$), with no difference between the two groups. Compared to a sham-NMES intervention, a six-week home-based NMES program applied to the quadriceps of the nonoperative side early after ACL reconstruction prevented the occurrence of knee extensor muscle weakness six months after surgery. The authors concluded that nonoperative-side NMES may help counteract muscle weakness after ACL reconstruction. Limitations include small sample size, and NMES use was not fully controlled due to home-based administration of both interventions. Further research is needed to determine the clinical relevance of these findings.

The single-center, retrospective study by Ji et al. (2019) analyzed the effectiveness of NMES for pain relief caused by necrosis of the femoral head (NFH). The study included 80 participants with NFH who were assigned to a treatment group (n = 40, 25 males, mean age 42.3 years) that had received ibuprofen and NMES or to a control group (n = 40, 21 males, mean age 39.7 years) that received ibuprofen only, with treatment lasting for a total of six weeks in both groups. The authors reported that participants in the treatment group showed more effectiveness in pain relief (as measured by the VAS and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) sub-pain scales); however, participants in the treatment group did not show better outcomes in stiffness (as measured by the WOMAC sub-stiffness scale), and function (as measured by the WOMAC sub-function scale) than participants in the control group. Limitations include the short treatment duration and follow up, the lack of randomization, the retrospective design, the small sample size, and the single-center population source. The authors concluded that NMES may be helpful for pain relief in patients with NFH after six weeks of treatment.

In a single-center, open label, feasibility RCT by Wainwright et al. (2018), the potential role of NMES in preventing the formation of edema following THR was investigated. The study included 40 adults scheduled to undergo elective THR who were randomized to wear either the geko™ NMES device (n = 20, 14 females, age 67.2 ±9.2 years) or Saphena® anti-embolism compression stockings (n = 20, five female, age 67.8 ±11.9 years) continually from post-surgery until discharge. The primary outcome measure was the presence of lower limb edema, which was assessed by taking measurements of the circumference of the ankle, knee and thigh on the operated leg and the non-operated leg prior to surgery, post-operatively, at two days post-operatively and every day until discharge. The authors reported that there were no significant differences between the pre-operative swelling measurements at the ankle, knee, or thigh between the operated and non-operated legs, or between the pre-and post-operative swelling measurements at the ankle, knee, or thigh in the non-operated leg in either group. The authors reported that the NMES group had significantly less edema at the knee and thigh while the ankle circumference increased more in the compression group than the NMES group, but it was not statistically significant. Limitations of the study include the single-center design, the small sample size, and the heterogeneity between the two study groups. The authors concluded that the study suggested that NMES was a safe and well tolerated alternative to compression stockings and that NMES should be considered as part of a DVT prophylaxis.

Talbot et al. (2017) conducted a pilot RCT (NCT00942890) to compare the effects of a home-based NMES rehabilitation program plus the traditional military amputee rehabilitation program (TMARP) vs. the effects of TMARP alone on quadriceps muscle strength, functional mobility, and pain in military service members after a combat-related lower extremity amputation. In total, 44 participants with a unilateral transtibial amputation were randomly assigned to the TMARP plus NMES (n = 23) or to TMARP alone (n = 21). Both groups received 12 weeks of the traditional amputee rehabilitation, including pre- and post-prosthetic training. Those in the NMES group also received 12 weeks of NMES. Participants were tested at three-week intervals during the study for muscle strength and pain. For functional measures, they were tested after receiving their prosthesis and at study completion (weeks six and 12). In both groups, residual limb quadriceps muscle strength and pain severity improved from baseline to 12 weeks. The NMES plus TMARP group showed greater strength than the TMARP alone group at three weeks, before receiving the prosthesis. However, six weeks post-prosthesis, there was no group difference in the residual limb strength. Functional mobility improved in both groups between weeks six and 12 with no difference between the two treatment groups. The authors concluded that a home-based NMES intervention with TMARP worked at improving residual limb strength, pain, and mobility. While NMES seemed most effective in minimizing strength loss in the amputated leg pre-prosthesis, further research on amputation rehabilitation is warranted, as NMES may accelerate recovery.

In a prospective, longitudinal RCT, 66 participants, aged 50 to 85 years and planning a primary unilateral total knee arthroplasty (TKA), were randomly assigned to receive either standard rehabilitation (control) or standard rehabilitation plus NMES applied to the quadriceps muscle (initiated 48 hours after surgery). The NMES was applied twice daily at the maximum tolerable intensity for 15 contractions. Data for muscle strength, functional performance, and self-report measures were obtained before surgery and 3.5, 6.5, 13, 26, and 52 weeks after TKA. At 3.5 weeks after TKA, significant improvements with NMES were found for quadriceps and hamstring muscle strength, functional performance, and knee extension AROM. At 52 weeks, the differences between groups were attenuated, but improvements with NMES were still significant for quadriceps and hamstring muscle strength, functional performance, and some self-report measures. The authors concluded that the early addition of NMES effectively attenuated loss of quadriceps muscle strength and improved functional performance following TKA. The effects were most pronounced and clinically meaningful within the first month after surgery but persisted through one year after surgery. Further research focused on early intervention after TKA is warranted to continue to optimize patient outcomes (Stevens-Lapsley et al., 2012).

There are also studies that NMES can be effective when used for quadriceps strength training following anterior cruciate ligament (ACL) reconstruction or prior to TKA. In a small RCT of NMES for quadriceps strength training following ACL reconstruction, the group that received NMES demonstrated moderately greater quadriceps strength at 12 weeks and moderately higher levels of knee function at both 12 and 16 weeks of rehabilitation compared to the control group (Fitzgerald, 2003).

Nervous System Conditions

Cerebral Palsy (CP)

Abd Elmonem et al. (2024) conducted a randomized comparative trial to compare the effects of NMES combined with interrupted serial casting (SC) versus serial casting alone on various aspects of lower limb function in children with diplegic CP. The study included 33 children who were randomly assigned at recruitment to receive SC with a customized physical therapy program (Group A), or who received the same SC and customized physical therapy program along with NMES applied through cast windows during casting. Evaluations conducted before and after eight weeks of intervention were based on ROM, the Modified Tardieu Scale, handheld dynamometer measurements, and the Observational Gait Scale. The authors reported that both groups showed significant improvements in dorsiflexion ROM, popliteal angle, gastrocnemius dynamic spasticity, and hamstring dynamic spasticity after the intervention; however, significant differences were seen in dorsiflexor strength, knee extensor strength, and observational gait scale score between groups after the intervention, favoring group B. The authors concluded that the use of NMES during SC in children with diplegic CP may help overcome the substantial decrease in strength resulting from casting and may lead to less reduction of tone, improvement in ROM without significantly decreasing strength and achievement of greater improvements in gait function.

In a scoping review of 26 interventional studies and seven review articles, Greve et al. (2022) assessed the application of NMES to augment lower extremity exercises, and the effects of NMES on neuromuscular impairments and function for people with spastic CP. The 26 intervention publications included a total of 558 individuals aged three to 57 years with CP. The review included studies on three NMES applications including NMES-assisted strengthening (14 studies), NMES-assisted gait (11 studies), and NMES for spasticity reduction (seven studies). NMES-assisted strengthening included the use of therapeutic exercises and cycling while NMES-assisted gait included the use of NMES to improve gait patterns and NMES-spasticity reduction included the use of transcutaneous electrical stimulation or NMES to decrease tone. The authors stated that the findings of their scoping review indicated that NMES applied to strengthening exercise, gait and spasticity reduction demonstrated potential benefits for improving muscle physiology, neuromuscular impairments, gait patterns and functional mobility in individuals with spastic CP. The authors noted that the dosage of NMES intervention varied by study as did the exercise activities, NMES devices used, frequency and intensity parameters and they recommended further research to determine optimal protocols and dosage for NMES. The authors concluded that NMES was found to improve muscle structure, strength, gross motor skills, gait kinematics, walking speed and distance and reduced spasticity and that the use of NMES-assisted strengthening with therapeutic exercise and cycling, NMES-assisted gait, and NMES for spasticity reduction supports the use of NMES to improve mobility in people with spastic CP.

Rocha et al. (2022) conducted a systematic review of randomized clinical trials (RCTs) to evaluate the safety and efficacy of non-surgical interventions for the treatment of masticatory muscle spasticity in individuals with CP. The authors conducted a comprehensive search in the following databases: MEDLINE, Embase, Cochrane Library, LILACS, BBO, PEDro, Clinicaltrials.gov and WHO/ICTRP, without date and language restrictions. RCTs evaluating non-surgical interventions were considered. Primary outcomes such as masticatory function and adverse events were planned to be assessed. The risk of bias assessment was performed using the Cochrane risk of bias tool. The certainty of the evidence was assessed using the GRADE approach. Three RCTs assessing the effects of botulinum toxin, functional masticatory training, and neuromuscular electrostimulation (NMES) were included. Evidence with a very low certainty showed: (i) no difference between botulinum toxin and placebo regarding maximum chewing strength, chewing efficiency and global oral

health scale; (ii) improvement in masticatory function in favor of functional masticatory training versus conventional exercises, and (iii) in favor of strengthening exercises plus NMES versus placebo. All studies reported the blinding of the outcome as sessors and were of low risk of bias for this domain. No losses were reported from participants in any of the included studies. The authors concluded there was insufficient evidence to support the use of botulinum toxin and masticatory muscle strengthening programs alone and associated with NMES for the treatment of masticatory muscle in individuals with CP. The clinical decision must be individualized, and further studies are needed to support or refute the use of different non-surgical interventions for CP. This systematic review is limited by its small sample size (three RCTs), heterogeneous groups, and a lack of a controlled comparator group. Further research with randomized controlled trials is needed to validate these findings.

Cobo-Vicente et al (2021) performed a systematic review and meta-analysis to analyze the effect of NMES on skeletal muscle and on biomechanics of movement, functional mobility, strength, spasticity, muscle architecture and body composition of children and adolescents with chronic neurological disorders (CNDs) and chronic diseases. Their review consisted of 18 studies (including the Pool et al. study below) of which 15 were RCTs, two were non-RCTs, and one was a cross-sectional study. There were 595 participants between three and 14 years of age, of which 49% were female. Most of the studies (88.9%) included in the review were about CP (16 articles). There was also one study on spinal muscular atrophy and one study about obstetric brachial plexus injury. All the studies used NMES as their main intervention with the NMES programs lasting from four to 48 weeks in duration with an average application of 14 weeks. Half of the programs were home-based programs and half of the cases indicated the NMES was applied by professionals. The authors concluded that the use of NMES programs for children with CNDs, specifically CP, appears to be effective in improving strength, biomechanics of movement, and functional mobility; however, they noted that there were not enough studies to confirm that NMES produces benefits on spasticity, muscle architecture, and body composition. This study noted that there was little agreement in the variables analyzed in the different studies which made it hard to compare results and perform the statistical analysis of some variables. It also identified that there were small sample sizes in most of the studies and that, since most of the studies were focused on CP, the conclusions would be difficult to expand to other types of CNDs. The authors recommend future RCTs focusing on analysis of the effect of NMES on spasticity, muscle architecture and body composition in children with CNDs and that further research is needed to evaluate the effectiveness of NMES in pediatric patients with other chronic diseases.

An RCT by Pool et al. (2016) evaluated whether NMES applied to the ankle dorsiflexors during gait improves muscle volume and strength in children with unilateral spastic CP. The study involved 32 children (mean age of 10.5 years) and a Gross Motor Function Classification System of I or II. Participants were randomly assigned to either the 8-week daily NMES treatment group or control group (usual or conventional treatments). Outcomes at week eight (post-NMES) and week 14 (carryover) included magnetic resonance imaging for muscle volumes (tibialis anterior, anterior compartment, and gastrocnemius), strength (hand-held dynamometry for isometric dorsiflexion strength and heel raises for functional strength), and clinical measures for lower limb selective motor control. At week eight, the treatment group demonstrated significantly increased muscle volumes and dorsiflexion strength not only when compared to their baseline values but also when compared to the control group at week eight. At week 14, both tibialis anterior and lateral gastrocnemius volumes in the treatment group remained significantly increased when compared to their baseline values. However, only lateral gastrocnemius volumes had significantly greater values when compared to the control group at week 14. There were no between group differences in the clinical measures for lower limb selective motor control at weeks eight and 14. The authors concluded that eight weeks of daily NMES-assisted gait increases muscle volume and strength of the stimulated ankle dorsiflexors in children with unilateral spastic CP. These changes are use-dependent and do not carry over after the eight-week treatment period. Gastrocnemius volume also increased post-treatment with carryover at week 14.

Cerebral Vascular Accident (CVA)

Oh et al. (2023) conducted a systematic review and meta-analysis to examine the effectiveness of mirror therapy (MT) and NMES therapy on lower extremity motor function recovery, including walking speed, spasticity, balance, and other gait parameters in participants recovering from CVAs. The study included six RCTs (five parallel studies and one crossover study) that evaluated the use of a combination of MT and NMES therapy on patients who had experienced a CVA and that assessed the outcomes of lower extremity motor function and impairment. There was a total of 181 participants (52% male) who had experienced hemiplegia at any stage of stroke and exhibited various degrees of impairment in the motor function of lower extremities (91 in the treatment group who received MT + NMES and 90 in the control group who underwent conventional therapy with or without sham therapy). The authors reported that MT combined with NMES resulted in greater improvement relative to control group in walking speed, cadence, step length, and stride length but not in spasticity. The quality of evidence was reported by the authors to be moderate for the assessment of walking speed, low quality for balance and gait parameters, and very low quality for spasticity. Limitations of the study include the small number of participants in the included RCTs, the small number of participants in the sub-analysis groups, the inclusion of participants from multiple levels of recovery, and the short follow-up periods for the included

studies. The authors concluded that MT combined with NMES may be a suitable supplemental intervention to conventional therapy in patients who survive CVAs.

Wang et al. (2023) conducted a systematic review and meta-analysis to evaluate the clinical efficacy of NMES in patients with post-stroke dysphagia. Their study included 46 RCTs with a total of 3,346 participants with post-stroke dysphagia. There were 1,679 participants who received NMES plus swallowing therapy (ST) and the other 1,667 participants received just ST. The treatment course range was from two to 12 weeks. The authors stated that the meta-analysis showed that NMES combined with routine swallowing therapy (ST) could effectively improve swallowing function and the QOL, increase the upward and forward movement distances of the hyoid bone, reduce the rate of complications, and improve the swallowing function of participants with post-stroke dysphagia. The authors also stated that subgroup analyses found that participants with an onset of less than 20 days and who are older than 60 years of age appeared to have more positive effects after treatment and that a course of treatment of four weeks or less might achieve more satisfactory clinical efficacy than a course of more than four weeks. Limitations of the study included the predominance of studies being from one country (China), the heterogeneity of the NMES treatment protocols, the lack of clarity in most of the RCTs of the blinding method, and the lack of reporting of adverse events in most of the studies. The authors recommended more large-sample, high-quality, multi-center studies to strengthen the data on adverse events and to prove the clinical efficacy of NMES and ST in the treatment of post-stroke dysphagia.

In a single-center, randomized, self-controlled, cross over study with 35 participants with post-stroke dysphagia, Zhang et al. (2022) reported that participants demonstrated improved Modified Barium Swallow Impairment Profile and Penetration-Aspiration Scale scores when NMES was applied. Participants were considered eligible for inclusion if they were adults between 18 and 80 years of age who had been diagnosed with stroke with dysphagia and scored below level 3 on the Modified Barium Swallow Impairment Profile-6 (BMSImP). To eliminate order effects, 17 participants received NMES first while the remaining 18 participants received sham stimulation first. A video fluoroscopic swallowing study (VFSS) procedure was initiated 30 seconds after each participant had fully adapted to real-NMES while the participant was fed three mouthfuls of mildly thick food over the five-minute stimulation period. The sham stimulation period was done with the same electrode placement and VFSS process, without the application of NMES. The authors reported that NMES significantly shortened oral transit time and improved initiation of the pharyngeal swallow while decreasing the risk of penetration and aspiration which may aid in early feeding training for patients with dysphagia following stroke. Limitations of the study include the small sample size, single-center design, and lack of blinding. The authors concluded that the results of this study suggested that NMES may aid in promoting early therapeutic feeding following stroke.

Miller et al. (2022) conducted a systematic review to evaluate the most recent studies regarding a potential effectiveness of neuromuscular electrical stimulation (NMES) as a treatment for oropharyngeal dysphagia. Eighteen studies were identified with varying participant groups, stimulation protocols, electrode placement and therapy settings. However, 16 studies have reported of beneficial outcomes in relation with NMES. The authors concluded that there is a considerable amount of level 2 studies which suggest that NMES is an effective treatment option, especially when combined with traditional dysphagia therapy (TDT) for patients with dysphagia after stroke and patients with Parkinson's disease, or with different kinds of brain injuries. Further research is still necessary in order to clarify which stimulation protocols, parameters and therapy settings are most beneficial for certain patient groups and degrees of impairment. Data pooling and statistical analysis could not be conducted due to the inhomogeneity of study protocols. Further research with randomized controlled trials is needed to validate these findings.

Ohnishi et al. (2022) conducted a randomized controlled trial (RCT) to investigate the effect of combined therapy with repetitive facilitative exercise (RFE) and neuromuscular electrical stimulation (NMES) on patients who had experienced a stroke with severe upper paresis. This study included a total of 99 participants with very severe paresis and with scores of zero or 1a in the Finger-Function test of the Stroke Impairment Assessment Set (SIAS). Participants were randomly divided into four groups, namely, NMES, RFE, RFE under NMES, and conventional training (CT) groups. A total of 20 minutes of group-specific training in addition to 40 minutes of conventional exercise per day, seven times a week for four weeks after admission, was performed. The upper extremity items of the Fugl-Meyer Assessment (FMA) were evaluated before and after the training period. The total score gains of the FMA, FMA wrist item, and FMA finger item were larger in the RFE under NMES group than those in the CT group ($p < 0.05$). The authors concluded that the combination of voluntary movement and electrical stimulation may promote the activation of paralyzed muscles and improve distal function for very severe paralyzed upper limbs. A limitation of this study was that the number of joint movement repetitions was arbitrary, although the training period of each group was defined. The authors suggest that additional studies are warranted to verify the effects of treatments with a fixed number of movements.

Xie et al. (2022) conducted a two-arm randomized controlled trial (RCT) to investigate the effects of simultaneous use of neuromuscular electrical stimulation on median nerve (m-NMES) and language training (m-NMES-LT) on cerebral oscillations and brain connection, as well as the effect on clinical efficacy following cerebrovascular accident (CVA). A

total of 21 right-handed adult participants with aphasia after stroke were randomly assigned to language training (LT) group (n = 10) and m-NMES-LT group (n = 11), and tissue concentration of oxyhemoglobin and deoxyhemoglobin oscillations were measured by functional near-infrared spectroscopy in resting and treatment state during three consecutive weeks. Five characteristic frequency signals (I, 0.6-2 Hz; II, 0.145-0.6 Hz; III, 0.052-0.145 Hz; IV, 0.021-0.052 Hz; and V, 0.0095-0.021 Hz) were identified using the wavelet method. The wavelet amplitude (WA) and wavelet phase coherence (WPCO) were calculated to describe the frequency-specific cortical activities. The m-NMES-LT induced higher WA values in contralesional prefrontal cortex (PFC) in intervals I, II, and V, and ipsilesional motor cortex (MC) in intervals I-V than the resting state. The wavelet phase coherence (WPCO) values between ipsilesional PFC-MC in interval III-IV, and between bilateral MC in interval III-IV were higher than resting state. In addition, there was a positive correlation between WPCO and Western Aphasia Battery in m-NMES-LT group. The authors concluded that the language training combined with neuromuscular electrical stimulation on median nerve could improve and achieve higher clinical efficacy for aphasia. This is attributed to the m-NMES-LT which could enhance cortical activation and brain functional connectivity in patients with aphasia, which was derived from myogenic, neurogenic, and endothelial cell metabolic activities. A small sample size 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.

A randomized controlled trial (RCT) was completed by Huang et al. (2021) to compare the effectiveness of contralaterally controlled functional electrical stimulation (CCFES) versus neuromuscular electrical stimulation (NMES) on motor recovery of the upper limb in subacute stroke patients. A total of 50 participants within six months post-stroke were randomly assigned to the CCFES group (n = 25) and the NMES group (n = 25). Both groups underwent routine rehabilitation plus 20-minute stimulation on wrist extensors per day, five days a week, for 3 weeks. Fugl-Meyer Assessment of upper extremity (FMA-UE), action research arm test (ARAT), Barthel Index (BI), and surface electromyography (sEMG) were assessed at baseline and end of intervention. After a three-week intervention, FMA-UE and BI increased in both groups ($p < 0.05$). ARAT increased significantly only in the CCFES group ($p < 0.05$). The changes of FMA-UE, ARAT, and BI in the CCFES group were not greater than those in the NMES group. The improvement in sEMG response of extensor carpi radialis by CCFES was greater than that by NMES ($p = 0.026$). The co-contraction ratio (CCR) of flexor carpi radialis did not decrease in both groups. No adverse events were reported during the intervention and follow-up in any of the groups. The authors concluded that CCFES improved upper limb motor function but did not show better treatment effect than NMES. CCFES enhanced the sEMG response of paretic extensor carpi radialis compared with NMES but did not decrease the co-contraction of antagonist. There are multiple limitations to this study. The central plasticity of subject was not evaluated by electrophysiological or functional imaging investigation at baseline, which could be a confounder of the treatment effect of CCFES. The effect of CCFES on central plasticity was not measured in this study, and the duration of intervention was short, which may reduce the effect of CCFES. The findings of this study need to be validated by well-designed studies, and further investigation is needed before clinical usefulness of this procedure is proven.

Kristensen et al. (2021) conducted a systematic review and meta-analysis to elucidate the effectiveness of neuromuscular electrical stimulation (NMES) toward improving ADLs and functional motor ability post stroke and to investigate the influence of paresis severity and the timing of treatment initiation for the effectiveness of NMES. The inclusion criteria were randomized controlled trials exploring the effect of NMES toward improving ADL or functional motor ability in survivors of stroke. The search identified 6,064 potential articles with 20 being included. Two independent reviewers conducted the data extraction. Methodological quality was assessed using the PEDro scale and the Cochrane Risk of Bias Tool. Data from 428 and 659 participants (mean age, 62.4 years; 54% male) for outcomes of ADL and functional motor ability, respectively, were pooled in a random-effect meta-analysis. The analysis revealed a positive effect of NMES toward ADL [standardized mean difference (SMD), 0.41; 95% CI, 0.14-0.67; $p = .003$], whereas no effect on functional motor ability was evident. Subgroup analyses showed that application of NMES in the subacute stage (SMD, 0.44; 95% CI, 0.09-0.78; $p = .01$) and in the upper extremity (SMD, 0.34; 95% CI, 0.04-0.64; $p = .02$) improved ADL, whereas a beneficial effect was observed for functional motor abilities in participants with severe paresis (SMD, 0.41; 95% CI, 0.12-0.70; $p = .005$). The authors concluded that the results of the meta-analysis are indicative of potential beneficial effects of NMES toward improving ADL post stroke, whereas the potential for improving functional motor ability appears less clear. Furthermore, subgroup analyses indicated that NMES application in the subacute stage and targeted at the upper extremity is efficacious for ADL rehabilitation and that functional motor abilities can be positively affected in patients with severe paresis. Limitations include a high risk of blinding and reporting bias. Further investigation is needed before clinical usefulness of this procedure is proven.

In a systematic review of RCTs, Alamer et al. (2020) evaluated the efficacy of NMES on swallowing function in patients who experienced a dysphagic stroke. The authors analyzed 11 RCTs that included studies that examined NMES, and/or NMES combined with conventional swallowing therapy irrespective of the duration of the intervention was provided or the outcome(s) measured. The studies included a total of 784 participants with a mean age of 54 to 66.2 in the treatment groups and 55.8 to 66.1 in the control groups. The mean duration since stroke was 15.7 hours to 35.4 weeks in the

treatment groups and 16.0 hours to 36.0 weeks in the control groups. The RCTs compared the effectiveness of NMES, and/or conventional swallowing therapy with controlled group; conventional swallowing therapies, and/or placebo/sham stimulations were considered. The reviewers used the Physiotherapy Evidence Database (PEDro) scale and determined that the overall methodological quality of the evidence was ranged from moderate to high. The authors concluded that NMES along with traditional swallowing therapy could be an optional intervention to improve swallowing after stroke; however, they noted that great attention is needed regarding the course of disease duration and its severity when NMES is used for post-stroke dysphagia. The authors were not able to perform a meta-analysis due to the heterogeneity of the interventions. They recommended future research be conducted on NMES efficacy on chronic stroke patients with swallowing dysfunction.

Knutson et al. (2016) evaluated whether contralaterally controlled FES (CCFES) or cyclic NMES (cNMES) was more effective for post-stroke upper limb rehabilitation in an interventional, phase II, randomized trial conducted at a single institution. Participants who had experienced a stroke (n = 80) with chronic (more than six months) moderate to severe upper extremity (UE) hemiparesis were randomized into two groups, receiving 10 sessions/week of CCFES- or cNMES-assisted hand opening exercise at home plus 20 sessions of functional task practice in the lab over 12 weeks. The primary outcome was improvement in Box and Blocks Test (BBT) score at six-months post-treatment, with UE Fugl-Meyer motor assessment (UEFMA) and Arm Motor Abilities Test (AMAT) also being measured. Evaluation of participants occurred at baseline, every three weeks during the treatment period, at end-of-treatment, and two, four, and six months post-treatment by a blinded assessor. At six months post-treatment, the CCFES group had greater improvement than the cNMES group on the BBT, 4.6 versus 1.8, respectively, and a between-group difference of 2.8. No significant between-group difference was found for the UEFMA or AMAT. The authors concluded that 12 weeks of CCFES therapy resulted in improved manual dexterity compared to cNMES in stroke survivors experiencing chronic moderate to severe hand impairment, with advantage given to those whose impairment was moderate and were less than two years post-stroke. The translatability of CCFES therapy to other research sites and to clinical practice still has not been established.

In an RCT by Shen et al. (2015), contralaterally controlled FES (CCFES) was compared to NMES as an innovative method to improve UE functions after stroke. Sixty-six participants were also treated with conventional medical treatment and rehabilitation training and were equally randomized into two groups. The treatments were administered in 20-minute sessions, five times per week for three weeks. Tools to assess results included the FMA, motricity index (MI), the Hong Kong version of functional test for the hemiplegic UE (FTHUE-HK) and active ROM (AROM) of wrist extension. Participant status was measured before and after three weeks of treatment. Both groups showed significant improvements in all the measurements after treatment. Participants in the CCFES group showed significantly higher UE FMA, FTHUE-HK scores and AROM of wrist extension than those in NMES group. The authors concluded that compared with the conventional NMES, CCFES provides better recovery of UE function in patients with stroke.

Lin et al. (2011) completed a single-blinded, RCT to investigate the long-term efficacy of NMES in enhancing motor recovery in the UEs of stroke patients. A total of 46 participants with stroke were assigned to a NMES group or a control group. Participants in the NMES group received the treatment for 30 minutes, five days a week for three weeks. Measurements were recorded before treatment, at the second and third week of treatment and one, three, and six months after treatment ended. The Modified Ashworth Scale for spasticity, the UE section of the FMA, and the Modified Barthel Index were used to assess the results. Significant improvements were found in both groups in terms of FMA and Modified Ashworth Scale scores after the 3rd week of treatment. The significant improvements persisted one month after treatment had been discontinued. At three and six months post-treatment, the average scores in the NMES group were significantly better than those in the control group. The authors concluded that three weeks of NMES to the affected UE of participants with stroke improved their motor recovery. One limitation of this study was the absence of a sham stimulation group. Future studies using similar stimulation protocols with a larger sample are needed to gain further insight into the potential to induce functionally beneficial neuroplasticity in stroke patients.

Respiratory System Conditions

In a systematic review and meta-analysis on the effectiveness of NMES in patients with chronic obstructive pulmonary disease (COPD) on mechanical ventilation (MV), Gutiérrez-Arias et al. (2022) concluded that NMES may improve functional independence and decrease MV time in adults with COPD. The study included four RCTs with a total of 144 adults (aged 18 years or older) with COPD who were hospitalized and received ventilatory support and who received NMES while on MV. Comparator interventions included studies that did not apply any intervention or that included sham electrical stimulation. Three of the studies were conducted in an acute critical care setting while the fourth study was conducted in a chronic critical care rehabilitation setting. The authors reported that the results of their review showed that NMES can improve functional independence in being able to move from bed to chair more quickly than was seen in participants with COPD who did not receive NMES and that participants with COPD who received NMES were on MV for a shorter period of time than was seen in participants with COPD who did not receive NMES. Limitations of the study include the heterogeneity of the NMES treatment and in the reporting parameters among the studies, the small number of

studies included and in the heterogeneity of the place of service in the included studies. The authors recommend future RCTs with better methodological design and for studies to assess duration of MV weaning, dyspnea, fatigue of lower limbs, functional exercise capacity at discharge, maximal exercise capacity at discharge and physical activity level at discharge.

Donadio et al. (2022) conducted a RCT to evaluate the effects of a supervised resistance-training program, associated or not with neuromuscular electrical stimulation (NMES), on muscle strength, aerobic fitness, lung function and QOL in children with cystic fibrosis (CF) presenting with mild-to-moderate pulmonary impairment. A total of 27 participants, aged between six and 17 years, were enrolled in this study. Subjects were randomly allocated to control (CON); exercise (EX); or exercise and NMES (EX + NMES) groups and evaluated at baseline and at the end of an eight-week individualized exercise-program (three days per week for 60 minutes per session). NMES was applied in the quadriceps and the interscapular region, simultaneously to the exercises. CON group followed the CF team recommendations. The main outcome measures were lung function, cardiorespiratory fitness, functional capacity, QOL, and muscle strength. No interactions were found for cardiorespiratory fitness. Functional capacity presented differences, indicating a better performance in both EX and EX + NMES. No changes between groups were seen for QOL and lung function. As for muscle strength, EX, and EX + NMES presented large effect sizes and differences, compared to CON, for quadriceps ($p = 0.004$, $\eta 2p = 0.401$), pectoral ($p = 0.001$, $\eta 2p = 0.487$), dorsal ($p = 0.009$, $\eta 2p = 0.333$) and handgrip ($p = 0.028$, $\eta 2p = 0.278$). The authors concluded a resistance exercise-training program led to improvements in muscle strength and functional capacity in participants with CF with mild-to-moderate pulmonary impairment. The addition of NMES to the training program resulted in no extra favorable effects. This study has limitations, including the difference in genotyping between groups. Although there is evidence to support that its effect on exercise variables is not substantial, it may have influenced present results. In addition, the mild-to-moderate impairment of the sample could also affect results, as smaller effects are expected in patients with a high aerobic fitness and lower muscular abnormalities. Further investigation is needed before clinical usefulness of this procedure is proven.

Wu et al. (2020) conducted a systematic review and meta-analysis to determine the effects of NMES on exercise capacity, functional performance, symptoms and HRQOL in patients with COPD. They reviewed 13 RCTs, of which seven studies explored the effect of NMES versus usual care and six studies compared NMES plus conventional exercise versus exercise training alone with or without sham training for NMES. Study participants totaled 447 adults with confirmed diagnosis of severe or very severe stable COPD. The authors noted no statistical increase in HRQOL among participants allocated with NMES and that NMES had no benefit for the peak rate of oxygen uptake and peak power. The authors stated that the results of the study showed there was insufficient evidence to support the positive effects exerted by NMES in COPD participants. The authors concluded that, based on current available data, NMES should not be regarded as a replacement for pulmonary rehabilitation completely, for the combination does not result in further improvement. The fundamental limitation noted by the authors was that the quality of the evidence in their meta-analysis was very low and limited by poor methodology leading to the risk of bias. Other limitations noted include the lack of blinding of the assessors and that estimates of random variability was present in only seven of the 13 studies. The authors recommend that future studies add the data describing the intrinsic muscle function or peripheral muscle force, and following up the adverse signs or events, in which NMES is applied alone or in isolation from rehabilitation strategies.

A 2018 Cochrane review by Hill et al. evaluated the effects of NMES, either alone or concurrently with conventional exercise therapy, to determine if this treatment might improve the overall physical condition and health related QOL in people with chronic obstructive pulmonary disease (COPD). Nineteen studies met the inclusion criteria, of which 16 contributed data on 267 individuals with COPD. Of these 16 studies, seven explored the effect of NMES versus usual care. Nine explored the effect of NMES plus conventional exercise training vs conventional exercise alone. The reviewers concluded that NMES, when applied alone, increased quadriceps force and endurance, six minute walking distance, time to symptom limitation exercising at a submaximal intensity, and reduced the severity of leg fatigue on completion of exercise testing. Evidence quality was considered low or very low due to risk of bias within the studies, imprecision of the estimates, small number of studies and inconsistency between the studies.

Miscellaneous Conditions

In a systematic review and meta-analysis, Alqurashi et al. (2023) sought to evaluate the effectiveness of NMES to prevent or reverse acquired disability of hospitalized patients. The systematic review included 42 published papers from 38 studies and 39 papers from 35 studies in the meta-analyses. There was a total of 1,452 adult participants (61% male, age range 19 – 86 years) included in the studies who had been hospitalized with acute medical, or acute or elective surgical conditions. The studies included 12 involving critical illness, 11 studies that involved post-surgery, four involved patients with COPD, six that involved patients with heart failure, two that involved patients with sepsis, and one each that involved spinal injury, COVID-19, and frailty. Delivery location of the NMES varied among studies with 21 studies in the ICU with two that continued NMES for the remainder of the hospital stay, and 17 studies that pertained to NMES delivered in hospital wards with six continuing NMES at home after discharge. Broad heterogeneity of the intervention duration existed

among studies both in length of time NMES was delivered per treatment as well as the range of days that NMES was delivered, the frequency of NMES stimulation and session frequency per week. Risk of bias was assessed as high in 17 studies, unclear in 13 studies, and low in eight studies. The authors reported that NMES had a small effect on muscle strength (pooled results from 21 RCTs with 816 participants), walking performance (15 studies with 723 participants) and on functional mobility (12 studies with 441 participants), and a moderate effect on muscle size (15 studies with 343 participants), The authors also reported that there was a small and non-significant effect on health-related QOL (six studies with 229 participants), that nine percent of participants reported undesirable experiences, and that the effects of NMES on length of hospital stay (six studies with 260 participants), and molecular and cellular biomarkers (nine studies) were unclear. The authors concluded that NMES was a promising intervention that might help reduce or prevent hospital-acquired disability. Limitations include the small sample sizes of most studies, and the moderate heterogeneity of the study designs, inclusion criteria, NMES protocols and participant populations. The Takino 2023 study below was included in this systematic review and meta-analysis.

Takino et al. (2023) conducted a multi-center, parallel, two-arm, sham-controlled, blinded RCT on the effect of NMES on postsurgical muscle weakness in older adults with diabetes mellitus who had undergone an elective cardiovascular surgery. The study included 180 adults who were randomly assigned to an NMES treatment group (n = 90) or to a sham group (n = 90). Participants in the NMES group received NMES from postoperative day one to postoperative day seven in daily sessions of 60 minutes. The isometric knee extensor strength (IKES), the usual walking speed (UWS), maximum walking speed (MWS) and grip strength (GS) were measured preoperatively and at postoperative day seven. The authors reported that the IKES showed less change (-2%) in the NMES group than in the sham control group (-13%) and that similar results were found in the percent change in MWS with significantly lower percent change in the NMES treated group than in the sham control group. The authors also reported that the findings were stronger in participants ≥ 75 years of age. The authors concluded that a short course of NMES (less than one week) administered to the lower extremity muscles immediately after cardiovascular surgery could mitigate postsurgical muscle weakness and functional decline in the study population.

Nonoyama et al. (2022) conducted a retrospective cohort study to examine the course of critically ill older patients treated with neuromuscular electrical stimulation (NMES) in the intensive care unit (ICU) and to define the impact of its use. This study was conducted using older ICU patients (≥ 65 years) categorized into a control group (n = 20) and an NMES group (n = 22). For subgroup analysis, each group was further classified into pre-old age (65–74 years) and old age (≥ 75 years). The control group showed a decrease in muscle thickness during ICU and hospital stay. The NMES group showed lower reduction in muscle thickness and showed decrease in muscle echo intensity during hospital stay, compared to the control group. NMES inhibited decrease in muscle thickness in the pre-old age group versus the old age group. The decreasing effect of NMES on echo intensity during hospital stay manifested only in the pre-old age group. The authors did not find differences in physical functioning between the NMES and control groups. Lower limb muscle atrophy reduces in critically ill older patients (≥ 65 years) with NMES and is pronounced in patients aged < 75 years. The authors concluded that the impact of NMES on the physical functioning of older patients in ICU needs to be further investigated. The study is limited by its retrospective observations. Well designed, comparative studies with larger patient populations are needed to further describe safety and clinical outcomes.

A systematic review and meta-analysis by Sun et al. (2020) evaluating the efficacy of transcutaneous NMES on suprahyoid muscle groups and on infrahyoid muscle groups for treatment of swallowing disorders determined that there was no firm evidence to conclude on the efficacy of NMES on swallowing disorders. The authors reviewed 11 studies consisting of eight RCTs and three quasi-RCTs involving 585 adults between the ages of 46 and 68.5 years from five countries with variable etiologies including stroke, traumatic brain injury (TBI), head and neck cancer and Parkinson disease. While most of the included studies were deemed by the authors to have low risk of bias for their design, eight of the 11 studies had small sample sizes (< 57 participants), and one study had the participants complete the treatment at home which contributed to high risk of bias. The reviewers deemed the quality of evidence overall was low to very low. Treatment duration, NMES frequency and intensity and traditional therapies as well as the swallowing function outcome measures differed across trials. Limitations that were noted by the authors included the considerable difference in patient characteristics, stimulation parameters and outcome measurements that contributed to the evident heterogeneity. They also noted that only three of the 11 studies provided limited evidence on long-term effectiveness and that their systematic review only included studies published in English which may cause bias. The authors recommended larger-scale and well-designed RCTs with attention paid to the most optimal NMES protocol (eligible participants, stimulation muscle groups, duration) and long-term effects of NMES be studied to reach robust conclusions about the efficacy of NMES on swallowing disorders.

Liu et al (2020) conducted a systematic review and meta-analysis evaluating the efficacy of the early use of NMES to prevent intensive care unit acquired weakness (ICU-AW). The study reviewed 11 RCTs (including the Patsaki et al. study below) where participants received NMES with routine treatments and nursing care and the control group was either

minimum intensity sham NMES and/or routine treatment and nursing care. The studies included 576 adults between the ages of 18 and 85 who received mechanical ventilation for at least 24 hours. The authors determined that the meta-analysis showed that NMES can improve muscle strength, shorten mechanical ventilation time, ICU length of stay and total length of stay, improve the ability of patients to perform ADLs and increase walking distance. They also noted that NMES does not appear to improve the functional status of ICU patients during hospitalization, promote early awakening of patients or reduce mortality. Limitations identified by the authors include the heterogeneity of the outcome indicators in the included studies, the risk of publication bias due to the small number of studies included, the inclusion of only studies published in English and Chinese, and that the adverse effects and cost-effectiveness of NMES were not assessed.

Patsaki et al. (2017) studied the effects of NMES along with individualized rehabilitation on muscle strength of ICU survivors. Following ICU discharge, 128 participants were randomized to either daily NMES sessions and individualized rehabilitation (NMES group) or to the control group. Muscle strength was assessed by the Medical Research Council (MRC) score and hand grip at hospital discharge. Secondary outcomes were functional ability and hospital length of stay. The authors found that NMES and personalized physiotherapy in ICU survivors did not result in greater improvement of muscle strength and functional status at hospital discharge. However, they concluded that NMES may be effective in this subset of patients, and that the potential benefits of rehabilitation strategies should be explored in larger numbers in future studies.

Clinical Practice Guidelines

National Institute for Health and Care Excellence (NICE)

In the NICE guideline on stroke rehabilitation in adults, the recommendation was made for further research to be conducted on the use of NMES for treatment of dysphagia before it can be recommended due to the potential high cost of the intervention, the size of the trials and the low quality of evidence. NICE noted that the current studies indicate that use of NMES for the treatment of dysphagia appeared to improve QOL, reduce dysphagia and chest infections and helped people return to a normal diet. The guideline also stated that the evidence on the effect of NMES on mortality was uncertain because of small trial sizes and short follow-up times.

NICE published a guideline for the management of knee osteoarthritis (OA) in which they concluded that NMES 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 transcutaneous NMES for oropharyngeal dysphagia in adults found current evidence on efficacy for adults with dysphagia after a stroke to be limited in quality and quantity although it may have potential benefit. They also noted that, for adults with dysphagia not caused by a stroke, there is insufficient evidence on efficacy to support the use of this procedure. NICE states that this technology should only be used with special arrangements for clinical governance, consent and audit or research; and encourages further research into transcutaneous NMES for this condition, which clearly documents indications for treatment and details of patient selection (2018).

American Heart Association/American Stroke Association (AHA/ASA)

In its Guidelines for Adult Stroke Rehabilitation and Recovery, the AHA/ASA state that NMES combined with therapy may improve spasticity, but there is insufficient evidence that the addition of NMES improves functional gait or hand use. The AHA/ASA guidelines are endorsed by the American Academy of Physical Medicine and Rehabilitation and the American Society of Neurorehabilitation (Winstein et al., 2016).

Interferential Therapy (IFT)

Studies related to IFT are insufficient to support the safety and efficacy of this treatment approach for musculoskeletal pain as the studies are mostly case series, comparison studies or RCTs with small sample sizes, heterogeneous study protocols and short-term results. More robust studies are needed to establish their effectiveness compared to established treatment options for musculoskeletal conditions.

Low Back Pain

Rampazo et al. (2023) conducted a systematic review and meta-analysis to assess the effectiveness of IFT in people with non-specific chronic low back pain (NSCLBP). The review included 13 RCTs with a pooled sample size of 1367 participants. The authors reported that the main results showed moderate-quality evidence and moderate effect sizes that IFT probably reduced pain intensity and disability compared to placebo immediately post-treatment but not at intermediate-term follow-up, while low-quality evidence with small effect size showed that IFT may reduce pain intensity

compared to TENS immediately post-treatment, but not for disability. The authors also reported that there is very low-quality evidence that IFT combined with other interventions may not further reduce pain intensity and disability compared to the other interventions provided in isolation immediately post-treatment. Limitations of the review included the variability in treatment protocols and study designs, the disproportionate number of females to males, and the heterogeneity of comparison therapies. The authors concluded that moderate-quality evidence showed that IFT was probably better than placebo for reducing pain intensity and disability immediately post-treatment in people with NSCLBP and they suggested that future trials were needed to investigate the IFT efficacy comparing to other interventions and when combined with other interventions. This systematic review and meta-analysis included the Espejo-Antúnez (2021) and Franco (2017) RCTs previously included in this policy.

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 six 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 three week study. Authors determined that selected electrical therapies (IFT, TENS < and high voltage ES) appear to be effective in treating chronic LBP.

To assess the influence of TENS and IFT on pain relief and to compare the analgesic efficacy of the two modalities, Grabiańska et al. (2015) studied 60 participants with LBP. The participants were equally and randomly divided into two groups. Depending on the groups, participants were given a series of ten 20-minute sessions over a two-week period using either IFT or TENS currents. In all participants, VAS and Laitinen modified scale were taken before and after treatment. At the end of the two 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 people 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 participants 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 six 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.

Disorders of the Knee

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 participants 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 five times a week for two 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 VAS, WOMAC, 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 two weeks and three months. The authors concluded that TENS and IFC reduced pain sensitivity as compared to the placebo groups in participants 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 RCTs in which IFC was applied to participants with knee osteoarthritis and the outcomes of pain scores or functional scales were assessed. Ten RCTs with 493 participants 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 WOMAC 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 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, ROM, and edema at days zero, five, and 30 and that IFT did not show to be an effective modality for pain management in participants 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 people 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 six 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 six 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 participants 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 participants 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 eight weeks. Subjects completed questionnaires at baseline and after two, four, and eight 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 participants 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

Hayes published an Evolving Evidence Review (EER) for the neo-GEN-Series System for treatment of neuropathic pain. In their report, Hayes stated that they did not find any relevant clinical studies, any relevant systematic reviews or professional society guidelines or practice statements that included the neo-GEN-Series system for neuropathic pain. They reviewed literature for their 2024 update and, again, did not find any published studies, systematic reviews, or practice guidelines (2023, updated 2024).

In a single-center, prospective RCT, Tugay and Kul (2023), evaluated the effectiveness of IFT on ROM of joint and shoulder pain, functional status, and QOL in patients with subacromial impingement syndrome and to compare IFT with TENS and sham IFT. The study included 52 participants who were randomized into 3 groups with group 1 (n = 17, males = 4, mean age 51.8 years) receiving IFT, group 2 (n = 18, males = 3, mean age 51.8 years) receiving TENS, and group 3 (n = 17, males = 2, mean age 49.1 years) receiving sham IFT with all participants also receiving hot pack and exercise treatments. Therapy was provided for three weeks, five times a week for 20 minutes for each session. All participants were evaluated before treatment (T0), at the end of the eighth treatment (T1), and at the end of treatment (T2) with the active ROM and VAS, the Arm, Shoulder, and Hand Problems Questionnaire for functional status, and Short Form-36 for quality of life. The authors reported that there was significant improvement in effects on all of the ROM, VAS and the Arm, Shoulder, and Hand Problems Questionnaire scores at T2 and on the scores in some sub-parameters of Short Form-36 in all groups; however, there was no statistically significant difference at T2 between the groups. Limitations of the study included the single-center design, the short follow-up period, and the small number of participants in each arm of the study. The authors concluded that IFT and TENS exhibited equivalent results regarding ROM, pain, function and QOL of patients with subacromial impingement syndrome with no significant difference between IFT and TENS, and that adding IFT or TENS to hot pack and exercise therapy did not result in any extra benefits.

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 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, five days a week for four 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 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 QOL 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 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 patients with MPS with upper trapezius myofascial trigger point. A total of 105 participants with an upper trapezius myofascial trigger point were randomly allocated to three groups, three 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 eight times during four 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 one 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 participants 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.

Clinical Practice Guidelines

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).

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 LBP with or without sciatica and stated that these modalities should not be offered for treatment of LBP 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 LBP 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 LBP or sciatica (2016, updated 2020).

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.

In a systematic review and meta-analysis, Bavarian et al. (2024) assessed the efficacy of MENS in treating myofascial pain of the masticatory muscles, The systematic review included four RCTs with a pooled population of 159 participants

(age range 13-60 years, 64.8% female) with a diagnosis of masticatory myofascial pain disorder and the meta-analysis included three RCTs with a pooled population of 140 participants. All studies used pain measured by the VAS score as a primary outcome. Duration of therapy ranged from five days to four weeks and outcome assessments were completed immediately after each treatment session. The authors reported that treatment with MENS showed an improved mean reduction in pain by an additional −0.57 points when compared to the control groups. Limitations of the systematic review and meta-analysis include the limited number of studies available for inclusion, the small total sample size, and the heterogeneity of the study designs such as inclusion criteria, therapy protocols, control group comparison therapies used, and follow-up periods. The authors concluded that evidence from the meta-analysis showed that MENS was an effective, non-invasive treatment option for use to reduce pain in patients with myofascial pain of the masticatory muscle and they recommended more robust RCTs with standardized protocols and larger sample sizes be conducted.

Jha et al. (2023) conducted a single-center comparative study to compare the effectiveness of TENS and MENS for the relief of masticatory muscle discomfort. The four arm study included 120 adults with a diagnosis of masticatory muscle pain who were divided into two groups of 60 participants (each having 36 males and 54 females; mean age 32.4 years, range 18 to 54). Groups I and II were further separated into two subgroups of 30 participants (Group I into subgroups A and B, Group II into subgroups C and D) based on their VAS scores with Groups 1A and 2C having VAS scores of one through five and Groups 1B and 2D having VAS scores of six through 10. VAS scores were also assessed each day and at one month following therapy. Group I participants received TENS and Group II received MENS with each participant receiving electrical stimulation for five consecutive days. Participants were instructed not to use any additional medications to manage their masticatory muscle pain for one month following the therapy. The authors reported that there was a considerable reduction in pain for subgroup D who were treated with MENS; however, for subgroups A and C, there was a comparable reduction in the VAS score for both groups treated with MENS and TENS therapy. When evaluating the mouth-opening improvement for the MENS and TENS groups, the authors reported that there was an instantaneous and sustained rise at the one-month recall from day zero and that, for the MENS group, however, a statistically significant improvement in mouth opening was observed starting on day three and persisted through one-month recall after MENS. The authors concluded that MENS provided a quicker and more effective pain relief when compared to TENS. The authors also found that paresthesia and tingling were two adverse effects of TENS that were not found with MENS; however, MENS and TENS were equally helpful at treating masticatory muscle discomfort as well as improving mouth opening. Limitations of the study include the single-center design, the limited sample size, and the short follow-up period.

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 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 participants 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.

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 (one non-RCT), shoulder pain (one RCT), elbow pain (one non-RCT), LBP (one RCT and two non-RCTs) and knee pain (including the Lawson and Ranker RCTs below and one 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 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 two 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 LBP 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 third 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 adults treated in their facility with adjuvant frequency-specific microcurrent (FSM) in addition to physical rehabilitation for 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 six 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 LBP; 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-arm, 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 ADLs. 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 eight 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 participants who were divided into two groups: 22 treated with MENS therapy and 19 with placebo. Treatment plan was three therapy sessions per week for four weeks. Primary outcomes measured included pain intensity, pain disability, and QOL at baseline, and the end of treatment, and four weeks post-treatment using standardized questionnaires. Participants with a minimum of 30% reduction in neuropathic pain score (NPS) were defined as therapy responders. After four weeks, only six of 21 participants 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 systematic review and meta-analysis, Tan et al. (2024) analyzed the efficacy and safety of perioperative transcutaneous electrical acupoint stimulation (TEAS) on postoperative pain and recovery. The review included 76 RCTs with 9,665 adults who received TEAS therapy as the sole intervention. Surgical subspecialties in the RCTs included urology/andrology (3), gynecology (12), breast surgery (6), cardiothoracic surgery (8), hemorrhoidectomy (1), otolaryngology (2), neurosurgery (7), head and neck surgery (5), abdominal surgery (24), orthopedic surgery (6), and hepatobiliary + gynecology surgeries (2). The authors reported that participants treated with TEAS experienced a reduction in cumulative analgesic (morphine equivalent) consumption based on their pooled analysis from six studies (TEAS: 187, control: 268) that showed cumulative intravenous morphine equivalent consumption in the TEAS group was lower than that in the control group. The authors also reported that rest pain scores at two, six, 12 and 24 hours postoperatively, a reduction in statistical importance was found at multiple time points within the first 24 postoperative hours based on their meta-analysis on 24 studies which showed that TEAS reduced the rest pain scores at two hours, 12 hours, and 24 h; however, although these results were statistically significant, the differences only at 12 hours surpassed the predesignated threshold for the clinical importance of 1.0 cm on the VAS. In their assessment on risk of bias, the authors reported that 10 studies (13.16%) had overall low bias risks, 61 studies (80.26%) had some concern about bias, and 5 studies (6.58%) had overall high bias risks. The authors concluded that use of TEAS resulted in lower pain reported by participants, less opioid consumption and higher QOL during the first 24 hours postoperatively; however, the authors recommended for more high-quality evidence studies be performed. Limitations of the study included the heterogeneity of the treatment protocols including frequencies, acupoints and times of intervention, the predominance of studies (n = 66) being done in one country, the heterogeneity of surgical procedures performed, and the lack of registered protocols or description of the randomization process in more than half of the studies.

Zhang et al. (2024) conducted a systematic review and meta-analysis to assess the evidence supportive of the use of TEAS for rehabilitation following TKA. The study included 20 RCTs with 1295 participants. The authors reported that TEAS improved several outcomes compared to control groups, including pain reduction, ROM, and scores on the Hospital for Special Surgery Knee Score (HSS), and the Knee Society Score (KSS) measurement tools. In their subgroup analysis, the authors found that TEAS had a significant reduction in pain postoperatively at six, 12, 24, 48 and 72 hours as well as at seven days and 14 days. Functional scores using the HSS and KSS also showed statistically higher scores in the TEAS group than in the control group as did the ROM scores. The authors conclude that the evidence indicated that the application of TEAS in patients undergoing TKA is related to postoperative pain alleviation, functional improvement, and fewer adverse events associated with analgesia. Limitations include the predominance of studies from one country, the heterogeneity of study designs including length of therapy, strength of stimulation and follow-up periods, as well as the lack of long-term follow up, and the small sample sizes and low quality of some of the studies. The authors recommended high quality large-sample, multi-center RCTS are needed to draw firmer conclusions.

Rodriguez Lagos et al. (2023) conducted a systematic review and meta-analysis to determine the effects of PENS and TENS on endogenous pain mechanisms in patients with musculoskeletal pain. There were 24 RCTs included in the qualitative analysis and 23 in the meta-analysis. Fourteen of the studies used TENS (1,136 subjects), 10 used PENS (808 subjects), and one used PENS and TENS (133 subjects). In the PENS studies, four used electroacupuncture, four used electrical intramuscular stimulation, and two electrical dry needling. Sixteen studies compared with a sham or placebo group, eight added one intervention and compared with that intervention, and two compared with a control group without intervention. With regard to the outcome measures, 23 measured local PPTs. Most studies conducted a single treatment session (n = 15), one included 16 treatment sessions, and the rest of the studies included between two and 10 sessions All studies measured the immediate results, eight studies measured short-term results, two measured mid-term results, and none measured long-term results. The authors reported that the immediate effects of PENS and TENS on local pressure pain thresholds (PPT) were significant with a moderate effect size and that, when the authors analyzed studies only with a lower risk of bias, the heterogeneity decreased and a decrease in the overall effect was also observed. The authors reported that the short-term effects on local PPTs were not significant when compared with the control group, and that both the mid-term effects on local PPTs and the immediate effects on conditioned pain modulation were significant with large effect size. The authors concluded that PENS and TENS have a mild to moderate immediate effect on local mechanical hyperalgesia in patients with musculoskeletal pain and that it appeared that these effects were not sustained over time. The authors also concluded that their analyses suggested an effect on central pain mechanisms that produced

moderate increases in remote PPT and an increase in conditioned pain modulation. Further studies by the authors were recommended to draw clearer conclusions.

Fernández-de-Las-Peñas et al. (2023) conducted a single-center, randomized parallel-group trial to compare the outcomes of the application of ultrasound-guided PENS targeting the median nerve versus surgery for improving pain and function in women with unilateral carpal tunnel syndrome (CTS). The study included 70 adult women who were randomly assigned to either receive PENS (n = 70, age 46 ±10 years) once a week for three weeks targeting the median nerve or undergo surgical / endoscopic decompression release of the carpal tunnel (n = 70, age 47 ±seven years). Primary outcome was hand pain intensity and secondary outcomes included functional status symptom severity, and self-perceived improvement. Outcomes were assessed at baseline and one, three, six, and 12 months after the end of the intervention The authors reported that their analyses showed an adjusted advantage for PENS at one and three months for mean pain, and at one, three and six months in worst pain intensity and in function. The authors also reported that both groups showed similar changes in symptom severity and reported similar improvement at 12 months in all outcomes. The authors concluded that PENS is as useful as surgery for treatment of CTS in women with CTS without denervation. The study was limited by the single-center design, the small sample size, the lack of a control group, and the lack of control for confounding variables.

In a single-center, prospective RCT that evaluated the safety and effectiveness of TEAS in postoperative analgesia following pediatric orthopedic surgery, Li et al. (2023) reported that those participants who received TEAS experienced significantly less postoperative pain and had reduced consumption of perioperative analgesia following surgery. The study included 58 children aged three to 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 two 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 two 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 hours 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 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 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 QOL 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 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 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 to 72 hours of the surgical procedure. Quality assessment of the included studies (as reported by the authors) resulted in seven trials being classified as low risk of bias, eight as unclear risk of bias, and one 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 to 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 could 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 EARB (2022) on the use of PENS for the treatment of LBP that there were no relevant newly published studies that met the inclusion criteria since they published their HTA on the subject in 2017 and archived it in August 2021. In the 2017 HTA, Hayes identified three 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 CLBP. The HTA noted that the results suggested a short-term (three 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 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 participants allocated to the sham group and 303 participants 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 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 participants 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 six 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 participants were randomly assigned to control group (n = 36) and treatment group (n = 35). Participants 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, participants in treatment group underwent 20 minutes of EA twice a day for five days. At baseline, day one, day three, and day seven 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 two 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 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 participants in the observation group were treated with TEAS from 30 minutes prior to anesthesia induction to the end of operation. The participants 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 participants affected by neuralgia were enrolled in the study and divided into three 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, one week, and one, three, and six months post-therapy. Perceived health outcome was measured with Euroqol-5-dimension (EQ-5D) questionnaire at baseline and at six 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 LBP with or without sciatica and stated that these modalities should not be offered for treatment of LBP 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 LBP, 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 LBP or sciatica (2016, updated 2022).

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.

Chogle et al. (2024) conducted a multicenter, prospective open-label registry of children who underwent PENFS for Disorders of the Gut-Brain Interaction (DGBIs) to explore the efficacy of PENFS as a standard therapy for DGBI. The study included 292 children between eight and 18 years of age (74% female, median age 16.3 years) who had functional dyspepsia (68%) and had failed four or more pharmacologic therapies (61%). The Rome IV Diagnostic Questionnaire on Pediatric Functional Gastrointestinal Disorders, the Abdominal Pain Index (API), the Nausea Severity Scale (NSS), and the Functional Disability Inventory (FDI) were completed at baseline and weekly during therapy with a subset of participants completing follow-up surveys every three months up to one year post-therapy. All participants were managed per standard practice conditions and data were collected for up to 12 weeks of consecutive PENFS therapy. The authors reported that the API scores improved significantly from a baseline of 2.88 to 1.99 at three weeks and further reductions were observed at three months and six months, the NSS scores similarly improved from baseline of 2.53 to 1.65 at three weeks and stayed significantly reduced at three and six months, and the FDI scores decreased across time from baseline of 20 to 12.0 at three weeks with scores staying persistently low at three months but not at six months. Limitations of the study included the lack of a control group, the inconsistent completion of the surveys, the high dropout rate during the first few weeks, the lack of long-term follow-up, the lack of control for any other interventions during the study, and the heterogeneity of the types of DGBI included in the study. The authors concluded that the study demonstrated the efficacy of PENFS for gastrointestinal symptoms and functionality for pediatric DGBI in a real-world setting.

In a prospective, observational study of the effect of auricular PENFS on QOL in children with, Chogle et al. (2023) included 31 children aged 11 -18 years (80.6% female) with DBGIs from a single-center institution. DGBIs included IBS (n = 13) and Functional Dyspepsia (FD; n = 9). Participants were evaluated for changes in gastrointestinal symptoms, QOL, functional disability, somatization, global health, anxiety, and depression using the API, the NSS, the FDI, the Child Somatization Inventory (CSI), and the Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health Anxiety, and Depression assessment tools. Medication use was reported by 83.9% of participants, with a median number of medications of five. Each participant received PENFS therapy once a week for four consecutive weeks for treatment of pain related DGBIs. The authors reported that participants reported significant reductions in abdominal pain, nausea severity, functional disability, somatization, and anxiety from baseline to week four after receiving PENFS therapy, while self-reported QOL and depression did not significantly change from baseline to week four; however, parents reported significant improvement in average QOL for their child in terms of physical function, psychosocial disability,

abdominal pain and somatization. The authors also reported that the number of medications participants were taking influenced several outcomes as those participants who were on three or more medications experienced significant decrease in anxiety, nausea severity and QOL physical functioning. Limitations of the study include the small sample size, the single-center design, the lack of objective measurement tools, the lack of long-term follow up, and the absence of a sham control group. The authors concluded that PENFS was a promising non-pharmacological treatment for pediatric patients with DGBIs, potentially leading to improvements in both symptom severity and QoL and recommended future research with larger sample sizes, placebo-controlled study designs and long-term follow up.

Santucci et al. (2023) conducted a retrospective study to examine changes in abdominal pain, nausea, and disability before and after treatment and to compare outcomes between treatments in children who met the Rome 4 criteria for functional abdominal pain disorders. The study included 101 patients between 11 and 21 years old who were treated with four weeks of PENFS (n = 49; median age 17 years; 75% female, 98% Caucasian), cyproheptadine (n = 31; median age 16 years, 90% female, 87% Caucasian) or amitriptyline (n = 21; median age 15 years, 52% female, 95% Caucasian). Outcomes were evaluated using the API, the NSS, and the FDI at baseline and follow-up within three months. In the PENFS group, 29 (59%) patients had been on medications but failed treatment and, therefore, received PENFS. These patients remained on a stable medication dose for the duration of treatment with PENFS. The authors reported that patients in the PENFS group had significantly lower scores on the API, NSS, and FDI at follow up, the patients in the amitriptyline group had significantly decreased API at follow-up but not NSS and FDI, and that patients in the cyproheptadine group did not change significantly on any of the three assessments. The authors concluded that therapy with PENFS showed improvements in abdominal pain, nausea, and disability while amitriptyline showed improvements in abdominal pain within three months of treatment, and that PENFS was more effective than cyproheptadine in improving abdominal pain and may be a good non-pharmacologic alternative for functional abdominal pain disorders. The study is limited by the homogeneity of the study population, the small sample size, the short follow-up period, and the lack of objective measurement tools.

In a single-center, open-label prospective clinical trial, Karrento et al. (2023) evaluated the effects of PENFS on pain, common comorbidities, and QOL in children with cyclic vomiting syndrome (CVS). The study included 30 children (60% female), eight to 18 years old, with drug refractory CVS. Each participant completed surveys at the beginning, at week six and at extended follow-up approximately four to six months later. Surveys included the 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 six weeks, but not at extended follow up. 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., four 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 two 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 EER by Hayes (2022, updated 2024) on the use of IB-Stim for the treatment of pain associated with irritable bowel syndrome (IBS) in adolescents was updated to include a review of abstracts for four newly published prospective pretest-posttest studies and stated that there is no change to their no/unclear level of support of the use of this device for this indication. The update indicated that there is longer-term follow-up (up to one year) since the initial publication of their 2022 review and that there is a new application of the technology being investigated, the use of IB-Stim for cyclic vomiting syndrome. In the 2024 update, Hayes still 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 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 three 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.

In a sub analysis of a cohort of patients who participated in a single-center, double-blind RCT, Krasaelap et al (2020) evaluated the efficacy of PENFS in adolescents with IBS. The study included 50 participants who met Rome III criteria for IBS who were randomly assigned to groups that either received PENFS (n = 27; median age 15.3 years; 89% female) or a sham stimulation (n = 23; median age 15.6 years; 91% female) five days per week for four weeks. Both groups were comparable in age, gender, body mass index, ethnicity, baseline pain (PFSD) and functioning FDI scores. Questionnaires were completed at baseline, after each week of therapy for weeks one through three and during an extended clinic follow-up visit eight to twelve weeks after end of therapy. Stool consistency was extracted from the Questionnaire on Pediatric Gastrointestinal Symptoms (QPGS) questionnaire and participants kept a daily diary during week 4 of therapy, noting if they had a bowel movement or not. The authors reported that reductions of 30% or more in worst abdominal pain were observed in 59% of participants who received PENFS versus 26% of participants who received sham stimulation and that participants who received PENFS had a composite pain median score of 7.5 versus 14.4 for the sham group, and a usual pain median score of 3.0 versus 5.0 in the sham group. The authors also reported that a symptom response scale score of two or more was observed in 82% of participants who received PENFS versus only 26% of participants in the sham group. The authors concluded that auricular neurostimulation reduced abdominal pain scores and improved overall wellbeing in adolescents with IBS and that PENFS is a noninvasive treatment option for pediatric patients with functional bowel disorders. Limitations of the study include the small sample size, the retrospective design, the short-term follow-up, and the incomplete assessment of stool frequency and consistency.

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 participants who discontinued treatment (one in the study group, seven in the sham group) and those who were excluded after randomization because they had organic disease (two and one in the study and sham groups, respectively), 57 participants in the PENFS group and 47 participants 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. Participants in the PENFS group had greater reduction in worst pain compared with sham after three 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.

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.

Hayes published an EARB that addresses PNS for the treatment of superior cluneal neuralgia (SCN). The Brief stated that there was not enough published peer-reviewed literature to evaluate the evidence related to PNS for treatment of SCN and that no clinical studies, or professional position statements or guidelines were found that addressed PNS for treatment of SCN (2024),

In their EER on Nidra for the treatment of restless leg syndrome (RLS), Hayes (2024) completed a full-text review of clinical studies and stated that there was minimal support for using the Nidra system for treatment of medication-resistant moderate-to-severe RLS. Hayes reviewed four fair-to very poor-quality clinical studies (two of which had overlapping populations and all four had the same research group perform the studies) that found the Nidra system was associated with clinically and statistically significant improvement in RLS symptoms from baseline and that, after two to 24 weeks of treatment with Nidra, 45% to 73% of patients achieved clinical response. Hayes stated that the minimal level of support also reflected that treatment response and symptom improvement were clinically and/or statistically significantly greater with Nidra than with sham treatment or no treatment and that adherence to treatment with the Nidra device was generally high. Hayes did not find any relevant systematic reviews or position statements or guidelines that pertained to the Nidra system.

Goree et al. (2024) conducted a multi-center, double-blind, randomized, placebo-controlled crossover trial to evaluate the effect of 60-day PNS treatment for addressing persistent postoperative pain after TKA. The study included 52 adults who were randomized to receive either active PNS (n = 28; 89.2% female; mean age 63.3 years) or placebo (n = 24; 75% female; mean age 62.2 years) stimulation. All study participants underwent placement of percutaneous leads targeting the femoral and sciatic nerves on the leg with postoperative pain. Leads were left in for eight weeks, with the primary outcome comparing the proportion of subjects in each group that reported ≥ 50% reduction in average pain compared to baseline during weeks five to eight post implantation. Participants had weekly follow-up visits to evaluate outcomes and progress and were observed until one month after lead removal (three months after start of treatment). Participants who received PNS were observed for another nine months, with visits at six, nine, and 12 months after start of treatment. Placebo group participants were allowed to crossover to receive PNS treatment or exit the study. If they elected to cross over, the placebo group participants underwent the same procedure as PNS participants and had follow-up visits at two, four, and eight weeks after start of treatment with leads removed at eight weeks, underwent observation for 12 months after start of active treatment, with follow-up visits at three, six, nine, and 12 months. The authors reported that 60% of participants in the PNS treatment group responded with a ≥ 50% pain relief relative to baseline while the placebo group had 24% respond with a ≥ 50% pain relief relative to baseline, and that participants in the PNS group also walked a significantly greater distance at end of treatment than did the participants in the placebo group with a mean percentage improvement in walking ability at end of treatment of 47% in the PNS group while the placebo group experienced a decrease in walking ability of -9%.. The authors also reported that participants in the PNS group improved to 16 percentage points above threshold and into the range of healthy individuals whereas the walking ability of participants in the placebo group further decreased to 22 percentage points below threshold. Limitations of the study included the small study population, and the inclusion of participants with partial knee replacements, revision knee replacements and bilateral knee replacements only in the placebo group. The authors concluded that the study provided evidence that percutaneous PNS decreased persistent pain, which led to improved functional outcomes after TKA.

Parikh et al. (2024) conducted a systematic review to summarize the literature involving the efficacy peripheral nerve stimulation in orthopedic surgery. The review included 16 studies (knee pain in eight studies (n = 31 participants), shoulder joint pain in six studies (n = 23 participants), and foot pain in two studies (n = 11 participants)) with 69 adult participants. The studies evaluating knee pain applied PNS leads targeting the femoral nerve, sciatic nerve, auricular nerve, and/or saphenous nerve while the studies on the use of PNS for shoulder pain included the axillary nerve and suprascapular nerves. The authors reported that all of the studies demonstrated that PNS was effective in reducing pain, with one study reporting statistically significant results. The authors also reported that some studies also showed reduced opioid consumption; however, conclusions regarding opioid consumption in the setting of PNS could not be made. The studies included also were subject to selection bias and placebo effect, according to the authors, which can lead to confounding, and the absence of randomization and comparative methodologies with controls also hindered the formulation of conclusive findings. The authors concluded that PNS can be effective in managing postoperative or chronic pain in patients with orthopedic pathology. Limitations of the study include the lack of control groups or randomization, the

small sample sizes in the included studies, the heterogeneity of the included studies, and the low number of studies available for inclusion.

In an EARB on the efficacy of PNS for treatment of shoulder subluxation poststroke, Hayes (2023) did not find any published clinical studies, or positions statements or guidelines that met their criteria (studies evaluating the clinical utility of whether PNS improves health outcomes) that addressed the use of PNS for this indication. Hayes concluded that the lack of evidence appears to confer no or unclear support for PNS for the treatment of shoulder subluxation poststroke.

Hayes published a Clinical Research Response (2023) on the StimRouter Neuromodulation System for the treatment of chronic pain that included a review of abstracts of two studies, including one RCT and one single-arm study, that met the inclusion criteria (studies reporting the effect of StimRouter on pain perception and validations scores, changes in opioid usage or adverse events and were a clinical study of any design). Hayes did not find any systematic reviews meeting the inclusion criteria and based on their review of full-text clinical practice guidelines and position statements, there was no or unclear practice guidance support for PNS for managing chronic pain with a peripheral nerve origin.

Früh et al. conducted a multi-center, retrospective study to investigate the safety and efficacy of externally powered PNS systems targeting the saphenous nerve for the treatment of chronic intractable post-surgical knee pain refractory to a multimodal pain management paradigm. The primary diagnosis for knee pain that led to knee arthroplasty was osteoarthritis (76%), meniscus/cruciate ligament injuries (12%), fractures (8%) and injury of the nervus saphenous after stripping of the vena saphenous (4%). Outcomes were measured using a 10-point pain scale measuring pain intensity at rest and in motion. QOL with the SF-36 form12, quality of sleep with the Pittsburgh Sleep Quality Index (PSQI)13 and mood states with the short form of the General Depression Scale (ADS-K). Thirty-three patients (median age 58 years, 45.5% female) were implanted with a peripheral nerve stimulator targeting the saphenous nerve branches; however, six (18.2%) were explanted due to non-sufficient initial benefit from the therapy and two subjects were explanted due to wound infections. The authors included the remaining 25 patients in the study and reported that all of them had significant improvements in knee pain both during motion and at rest, QOL, mood quality and quality of sleep through six month follow-ups. The authors also reported that nine subjects underwent an additional 12 month follow-up visit and reported significant decrease in knee pain at rest and in motion. The authors reported that the participants also reported significant reduction in opioid medication intake from a median of 80 Morphine Milligram Equivalents (MME) preoperatively to 20 MME at three months and six months post-permanent implant. When the authors included the patients who initially did not benefit from the PNS system (“trial phase”) and those who had system explantations due to wound infections, their intention-to-treat analysis showed an overall success rate with a minimum pain improvement of 50% in 75.8% of all patients. Limitations of the study include the retrospective design, the small sample size, and the short-term follow-up. The authors concluded that externally powered PNS at the saphenous nerve branches is safe and effective for patients with chronic knee pain as short-term results were promising and showed considerable reductions in pain scores and opioid intake.

Gilmore et al. (2023) completed a prospective, multi-center case series of patients with 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, HRQOL, depression and patient global impression of change. The authors reported that 91% of participants experienced clinically meaningful improvement in at least one outcome after two months, 79% at five months 73% at eight months, 75% at 11 months and 77% at 14 months while 77% of participants experienced clinically meaningful improvement in two or more outcomes at two months, 63% at five months, 60% at eight months, 59% 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 two 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.

Hayes published an EARB on the Nalu Neurostimulation System for treatment of chronic pain of peripheral nerve origin (2023) which indicated that they did not find any published peer-reviewed studies related to the Nalu Neurostimulation System and that, while they did identify two clinical practice guidelines and position statements, neither supported the use of implantable peripheral nerve stimulators for treatment of chronic pain.

In their HTA on percutaneous PNS for the treatment of intractable chronic pain in adults, Hayes (2022, updated 2024) identified and reviewed four studies (two RCTs and two 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 QOL, ADLs 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. Hayes noted in their 2024 update that no relevant newly published studies that met their inclusion criteria were found since the report was published in 2022.

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 (three studies), phantom limb pain (three studies), shoulder pain (two studies), post-surgical pain (two studies) and mononeuropathies (five 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 participants experienced at least a 30% reduction in pain and that it was common for participants 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 EER 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 three 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, updated 2023) that focused on safety and efficacy for PNS's ability to treat chronic pain and how it compared with other chronic pain management conditions. The 2023 update include three systematic reviews (that included mostly small RCTs and case series) and four additional low-quality case series. ECRI stated that larger RCTs are needed that include comparisons of PNS to other chronic pain management methods as the current studies have high heterogeneity which makes it difficult to permit firm conclusions.

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.

Öztürk et al. (2024) conducted a single center, retrospective, comparative study to investigate the effect of PEMF therapy added to routine physical therapy on pain and functional status in patients with CLBP. The study included 69 adults (mean age 49.2 years, 61.8% female) with CLBP who were divided into two groups with 34 in the group who received a standard regime of lumbar TENS, infrared, and ultrasound treatments, and 35 in the group who received the standard regimen in addition to PEMF. Patients were evaluated using the Quebec Back Pain Disability Scale (QBPDS) in terms of functional capacity and effects of LBP and the VAS for pain both before and after treatment. There was no significant difference detected between the two groups' pretreatment VAS and QBPDS scores. The assessments were conducted by the same physiatrist before therapy, the third week after treatment, and the twelfth week after treatment. The authors reported that, while the second and third measurement scores of both groups were significantly lower than their first-measurement VAS and QBPDS scores, the second and third-measurement scores of the PEMFT group were significantly lower than those of the control group and the effect size of the difference was large. Limitations of the study include the small sample size, the single center design, the short follow-up period, the retrospective study design, and the use of self-reported assessment tools. The authors concluded that PEMF appeared to be able to alleviate pain intensity and ameliorate disability in patients with CLBP and that it can be considered an effective and safe option that can be added to routine physical therapy modalities although the authors recommended further prospective, randomized studies to validate the effectiveness of PEMF.

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 VAS 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 participants 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 participants 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 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 MusiQol Questionnaire. Data were collected at baseline, after the four week protocol period, and at three 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 three 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 participants undergoing medial UKA were randomized into a control group (n = 36) or an experimental PEMFs group (n = 36). The participants allocated to the experimental group were instructed to use PEMFs for four hours per day for 60 days. They were evaluated before surgery and then during the time points corresponding to one month, two months, six months, 12 months, and 36 months after the surgery. No placebo group was included in the RCT. Clinical assessment included the 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 six ($p = 0.0297$), 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 participants using NSAIDs in the PEMFs and control group were 71% and 92%, respectively ($p = 0.0320$). At the two months point, 15% of the participants 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 six ($p = 0.0204$), 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 two ($p = 0.0073$), six ($p = 0.0006$), 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 (one month: $p = 0.0295$; two months: $p = 0.0012$; six months: $p = 0.0001$; 12 months: $p < 0.0001$; 36 months: $p = 0.0061$). 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 two, 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 three 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 two, 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 participants 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 QOL 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 participants 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 participants (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 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 six weeks so two different treatment durations (< four weeks and four to six 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 four to six 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 (≤ six 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 (PEF) 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 participants 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 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 QOL). 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 (four to 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, three 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.

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).

Restorative Neurostimulation

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

Gilligan et al. (2024) conducted a prospective five-year longitudinal follow-up of the ReActiv8-B pivotal trial (included below, Gilligan 2022) to evaluate the long-term outcomes of the use of restorative neurostimulation for the treatment of moderate-to-severe, disabling, refractory, predominantly mechanical CLBP by comparing their baseline data from the VAS, the ODI and the EuroQol's "EQ-5D-5L" index to their data collected at five years post implantation. Five year data was available for 126 of the original 204 participants (mean age 47 years; 54% female) in the original RCT with crossover study. . The authors reported that LBP VAS had improved from 7.3 to 2.4 cm, while 89 of 124 participants (71.8%) of participants had a reduction in pain of at least 50%, that the ODI improved from 39.1 to 16.5 with 77 of 126 participants (61.1%) of participants having a reduction of at least 20 points and that the EQ-5D-5L index improved from 0.585 to 0.807. The authors also reported that 46% of the 52 participants discontinued use of opioids and 23% decreased their intake of opioids over the five year follow-up period. Limitations of this follow-up study include the lack of a sham control group (due to crossover), the loss of participants to follow-up and the number of explants (62/30%) since the study began. The authors concluded that restorative neurostimulation safely provided clinically substantial and durable benefits in patients with refractory CLBP associated with multifidus muscle dysfunction.

Thompson et al. (2023) conducted a three year open label prospective follow-up for the treatment of CLBP of nociceptive origin with restorative neurostimulation. The study participants completed assessments for pain (NRS), disability (ODI) and health-related QOL (EQ-5D-5L) with outcomes collected at 45, 90, and 180 days and at one, two and three years after the activation visit with 33 (79%; mean age 47.7 years, 36.4% female) of the original 42 (mean age 47.2 years; 40% female) available at the three year appointment. The authors reported that baseline data included a mean NRS of 7.0, a mean ODI of 46.6 and EQ-5D of 0.426, and that changes in pain, disability, and QOL at three-year follow-up demonstrated a statistically significant improvement with reductions in NRS scores (by a mean of 2.7), and ODI (to a mean score of 26.0) and an improved EQ-5D-5L index to 0.707. The authors concluded that the ongoing follow-up of this cohort continued to demonstrate that restorative neurostimulation provided a statistically significant, clinically meaningful, and durable response across pain, disability and QOL scores for participants with mechanical CLBP refractory to conventional management. Limitations of the study include the small sample size, the lack of a control group and blinding, and the heterogeneity of the study population.

In a follow-up study (including Ardeshiri 2022 study below), Ardeshiri et al. (2023) combined data from three clinical trials (ReActiv8-B, ReActiv8-C and ReActiv8-PMCF) with a combined 261 participants of the 333 participants that were involved in the original studies who had completed two year follow-up to examine the effect of restorative neurostimulation in an older demographic. The combined study population was divided into four cohorts of 65 participants based on age quartiles. Each cohort was classified by change in disability (ODI) or change in pain score (NRS/VAS) and assessed as a proportion of participants per group at each time point while HRQoL and EQ5D-5L was longitudinally compared with baseline. The authors reported that 62% of the oldest quartile (median age 60) had an improvement of 50% in pain and that 48% had a 15 point improvement in ODI while the entire population (median age of 49) had an improvement of 50% of pain in 65% of participants and 60% of the participants had a 15 point improvement in ODI. The authors also reported that HRQoL improved in the oldest quartile and the entire population and that all age quartiles improved statistically and clinically over baseline. The authors concluded that their aggregate analysis of the three studies provided an insight into the performance of restorative neurostimulation in an older population and that, when compared with a similar cohort of younger participants, there were not statistically or clinically significant differences. Limitations include the heterogeneity of the three included studies and their designs, the small cohort of participants in the older quartile, and the retrospective design of the study.

In a prospective, observational follow-up study of 204 implanted trial participants of the ReActiv8-B trial, Gilligan et al. (2023) evaluated the three-year effectiveness and safety of the ReActiv8 Implantable Neurostimulation System in patients with refractory, disabling CLBP. Data was collected using the LBP 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 participants 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.

Ardeshiri et al. (2022) recruited 44 consecutive patients with refractory, predominantly nociceptive axial CLBP to participate in a single-center, consecutive cohort study to evaluate the effectiveness of restorative neurostimulation to improve pain, disability and QOL. 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 (ODI), and QOL (5-level EuroQol 5-Dimension) were collected at baseline and three, six, and 12 months after activation. Forty (91%) of the 44 participants completed follow-up after one year of therapy; two participants withdrew from the study before completing one year of therapy, and two participants were unable to attend follow-up appointments due to the COVID-19 pandemic. The authors reported that 68% of participants had moderate (≥ 30%) reductions in pain, 52% had substantial (≥ 50%) reductions in pain, and 48% were remitters and had a pain score less than or equal to three, which is considered to be mild pain to pain-free after one year of therapy. No lead migrations were reported; however, one participant required revision due to lead fracture. The authors concluded that clinically meaningful improvements in pain, disability and QOL were achieved with restorative neurostimulation and that this therapy is a new treatment option for well-selected patients with refractory CLBP.

Hayes (2022) completed an HTA 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 two RCTs and two prospective pretest-posttest studies with follow-up periods of six months to one year. The report noted an overall very low-quality body of evidence with two fair-quality studies, one poor-quality study and one 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 QOL, ADLs and medication utilization

In an EER focusing on the ReActiv8 Implantable Neurostimulation System, Hayes (2022, updated 2024) completed a review of full-text clinical studies and found minimal support for using ReActiv8 for 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 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 through four to five years of follow-up. Hayes did not find any studies that compared ReActiv8 with an active comparator, and found only one systematic review that included a single study. Hayes found no professional society guidelines that specifically recommend ReActiv8, although Hayes stated that there was weak support for PNS of medial branch for treatment of CLBP based on the three of four evidence-based guidelines that support the use of PNS of the medial branch for this indication. Hayes concluded that the evidence was limited and available from only two studies which reported high attrition rates (ranging from 30% to 38%) and that data from several active trials may provide additional insight into the safety and efficacy of ReActiv8.

ECRI (2021, updated 2024) 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 four 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. In the 2024 update, four before-and-after studies were identified including one with five year follow up to the Gilligan 2022 study above and the other three were found to have enrolled few participants (n = 44, n = 53, and n = 42); however, the studies were found to be at high risk of bias due to lack of independent control groups and/or single-center focus. ECRI also noted that the patient population in the Gilligan follow-up study may have had a different patient population than the original group selected for the RCT because of attrition and the lack of continued randomization. ECRI recommended additional independent studies with outcome reporting that includes broader populations who are intended to receive treatment with ReActiv8.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 CLBP. This clinical trial was a prospective, single-arm study at nine sites in the United Kingdom, Belgium and Australia that included 53 participants 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 participants 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 participant 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 participants 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 CLBP 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 one 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 four percent serious adverse events rate, including six 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.

Chung et al. (2024) conducted a single-arm pilot study to assess the efficacy of scrambler therapy (ST) for treatment of pain and nonpain symptoms related to CIPN. The study included 10 patients (mean age 60.8 years; 50% male; 70% Caucasian) with moderate to severe CIPN symptoms for more than three months who were treated for six different cancer diagnoses. The participants were regularly taking a variety of pain medications for their CIPN-related pain at the time of study enrollment. Each participants underwent daily treatments of ST for 45 minutes per treatment for 10 consecutive weekdays over 2 weeks and were evaluated weekly for one month, then monthly for five more months. One participant stopped treatment after the fifth day due to a family emergency but completed the full six months of follow-up. The authors reported that the worst pain was reduced by six months and that, by the end of the treatment, there was an improvement from baseline in balance (64%), gait (62%), and activity (64%) with continual improvement at six months from baseline in balance (38%), gait (43%), and activity (45%). The authors also reported that symptoms of numbness, tingling, trouble walking, and disturbed sleep had significant improvements while pain medication use decreased by 70% at the end of treatment and by 42% at six months. Patient satisfaction was also reported to be high (82%), and the authors did not report any adverse events with ST treatment. Limitations of the study include the lack of a control group, the small sample size, the single-center design, the heterogeneity of cancer diagnoses and the use of multiple questionnaires that may have been a source of reporting bias. The authors concluded that the results of the pilot study supported the use of ST by demonstrating improvement in multiple domains of QOL for CIPN participants during an extended follow-up of six months and they recommended further large-scale prospective studies to confirm their findings.

Yoo et al. (2023) conducted a single-arm prospective pilot study to explore the long-term effects of ST in managing painful diabetic peripheral neuropathy (DPN). The study included nine participants (mean age 58 years, 34% female) who received 10 consecutive STs of 45 minutes every one to two days. The primary outcome was pain score as measured with the VAS at baseline, during ST, immediately after ST and at one, two, three and six months after ST. Secondary outcomes were Michigan Neuropathy Screening Instrument (MNSI), Semmes-Weinstein (SW) monofilament test, and Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scores, which were measured at baseline, immediately after ST, and at one, two, three and six months after ST. The authors reported that the VAS scores showed significant improvement at the eighth, ninth and tenth sessions during ST and one month after ST but not at two, three and six months post ST. The authors also reported that the MNSI self-report component score was decreased one month after the ST but there was no significant change thereafter, and that no significant changes in the MNSI examination component, SW monofilament test, and LANSS pain scores were observed during the study period. Limitations include the small sample size, the lack of a control group, and the lack of use of more objective measurement tools. The authors concluded that their preliminary data suggested that ST may have short-term effects and limited long-term effects on painful DPN, and they recommended further research to investigate the mechanism of action of ST.

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 seven RCTs with 287 adults (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 LBP 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 three 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 QOL in people with cancer through minimizing pain and opioid intake. A total of 80 participants with head, neck and thoracic cancer were included in the study. In both arms, participants 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 participants who were experiencing chronic neuropathic pain after unilateral burn injuries. The participants had moderate or greater chronic pain (a VAS score of five or higher), 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 two 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 two 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 and short duration of follow-up.

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 included RCTs (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 nine relevant clinical studies that met inclusion criteria: two RCTs, one quasi-RCT, and six single-arm studies, including one repeated measures time series, three pretest/posttest studies, and two retrospective database reviews. Hayes noted that a majority of these studies had limited follow-up of ≤ six 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 two 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 one 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 (mmTBI) and that it may also benefit those with MS and CP; 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 participants 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 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 one 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 three 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 five minutes 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 patients with mmTBI 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 patients mmTBI. 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 people 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 five-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 two through five of the study. The authors noted that participants in both the active and the control group had significant and clinically meaningful improvements in SOT composite score and the DGI. 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 (18-65 years old) 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 (two 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, as 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 22, 2024)

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 22, 2024)

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 22, 2024)

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 22, 2024)

Percutaneous Peripheral Nerve Stimulation (PNS)

There are several devices used for PNS such as the StimRouter Neuromodulation System, SPRINT PNS System, and the Freedom Peripheral Nerve Stimulator. 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 22, 2024)

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

PSFS and PNSF devices, such as the Bridge System (previously, the NSS-2 System), the DrugRelief® auricular stimulator, and the Sparrow Therapy System™ are approved by the FDA under the 510K review process. Additional information can be found on the FDA website using Product Code PZR :https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm. (Accessed August 22, 2024)

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 22, 2024)

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 22, 2024)

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, 2019 (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 22, 2024)

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 22, 2024)

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 CLBP 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 22, 2024)

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 website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed August 22, 2024)

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 22, 2024)

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/scripts/cdrh/cfdocs/cfPMN/denovo.cfm . (Accessed August 22,2024)

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Policy History/Revision Information

Date	Summary of Changes

04/01/2026	**Coverage Rationale**
	• Removed language indicating:
	  ○ Transcutaneous electrical joint stimulation is not considered medically necessary
	  ○ Neuromuscular electrical stimulation (NMES) and functional electrical stimulation (FES) are medically necessary in certain circumstances
	• Revised language pertaining to medical necessity clinical coverage criteria; removed reference to the:
	  ○ InterQual® Medicare: Post Acute & Durable Medical Equipment, Transcutaneous Electrical Joint Stimulation Devices (TEJSD) for transcutaneous electrical joint stimulation
	  ○ InterQual® Medicare: Post Acute & Durable Medical Equipment, Neuromuscular Electrical Stimulation (NMES) NCD for NMES and FES
	• Added language to indicate:
	Functional Electrical Stimulation (FES)
	  ○ FES is proven and medically necessary as a component of a comprehensive ambulation rehabilitation program in individuals with lower limb paralysis due to spinal cord injury (SCI) when all the following criteria are met:
	  ▪ Demonstration of intact lower motor units (L1 and below) (both muscle and peripheral nerves)
	  ▪ Muscle and joint stability for weight bearing at upper and lower extremities that can demonstrate balance and control to maintain an upright support posture independently
	  ▪ Demonstration of brisk muscle contraction
	  ▪ Demonstration of sensory perception sufficient for muscle contraction
	  ▪ Demonstration of a high level of motivation, commitment, and cognitive ability for device use
	  ▪ Ability to transfer independently
	  ▪ Demonstration of independent standing tolerance for at least 3 minutes
	  ▪ Demonstration of hand and finger function to manipulate controls
	  ▪ Post-recovery from SCI and restorative surgery of at least 6 months
	  ▪ Absence of hip and knee degenerative disease
	  ▪ Absence of history of long bone fracture secondary to osteoporosis
	  ○ FES is unproven and not medically necessary due to insufficient evidence of efficacy for treating any other indication not listed above
	Neuromuscular Electrical Stimulation (NMES)
	  ○ NMES is proven and medically necessary for treating any of the following indications:
	  ▪ Disuse muscle atrophy if:
	  – The nerve supply to the muscle is intact; and
	  – The disuse muscle atrophy is not of neurological origin but results from other conditions, for example casting, splinting, or contractures
	  or
	  ▪ When used as part of a comprehensive lower limb rehabilitation program following total knee arthroplasty; or
	  ▪ To improve upper extremity function in persons with partial paralysis following stroke when used as part of a comprehensive rehabilitation program
	  ○ NMES is unproven and not medically necessary due to insufficient evidence of efficacy for treating any condition not meeting the criteria above
	Medical Records Documentation Used for Reviews
	• Added language to indicate:
	  ○ Benefit coverage for health services is determined by the federal, state, or contractual requirements, and applicable laws that may require coverage for a specific service

Date	Summary of Changes
	○ Medical records documentation may be required to assess whether the member meets the clinical criteria for coverage but does not guarantee coverage of the service requested ○ The patient's medical record must contain documentation that fully supports the medical necessity for the requested services ○ This documentation includes but is not limited to relevant medical history, physical examination, and results of pertinent diagnostic tests or procedures ○ Documentation supporting the medical necessity should be legible, maintained in the patient's medical record, and must be made available upon request **Applicable Codes** • Removed HCPCS code E0762 • Revised description for HCPCS code E0721 • Removed notation pertaining to HCPCS code E0762 **Supporting Information** • Updated *Description of Services*, *Clinical Evidence*, and *References* sections to reflect the most current information • Archived previous policy version CS036IN.11

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, 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.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.