Vagus Nerve Stimulation (VNS) and Vagal Blocking Therapy

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DESCRIPTION

Implantable Vagus Nerve Stimulation

Vagus nerve stimulation (VNS) was initially investigated as a treatment alternative in patients with medically refractory partial-onset seizures for whom surgery is not recommended or for whom surgery has failed. Over time, the use of VNS has expanded to include generalized seizures, and it has been investigated for a range of other conditions including chronic heart failure, headaches, treatment resistant depression, essential tremor, fibromyalgia, tinnitus, obesity, upper limb impairment due to stroke and autism.

Seizures are considered paroxysmal disorders (i.e., characterized by abnormal cerebral neuronal discharge) and occur when there is errant electrical discharge activity in the brain. Seizures cause different physical symptoms depending on the location of the electrical activity in the brain. They may be mild to severe, ranging from causing slight tingling sensation or momentary confusion to causing complete loss of consciousness.

Classification and subtypes of seizures are commonly diagnosed by electroencephalography (EEG). The diagnosis of seizure requires that the clinician identify that the patient has had an epileptic seizure as opposed to some other type of paroxysmal event, and then establish the type of seizure(s).

Generalized seizures are further broken down into motor and non-motor (absence) seizures. Focal seizures are further subdivided based on level of awareness (aware, impaired awareness, or unknown awareness). Additionally, focal seizures are sub grouped into motor and non-motor seizures, based on signs and symptoms at onset. Additional descriptors for both generalized and focal seizures may be added based on specific motor or nonmotor symptoms. Focal seizures can also be more clearly described based on the elemental features (cognitive, automatisms, emotional or affective, motor, autonomic, sensory, laterality).

Epilepsies can be subdivided into generalized, focal, generalized, and focal and unknown (epilepsy based on seizure type).

- **Generalized epilepsy**: Epilepsy is considered generalized if the seizures originate at some point within, or rapidly engaged bilaterally distributed networks, which can be subcortical or cortical structures and are frequently both. Generalized seizures do not need to necessarily include the entire cortex, however, they may be asymmetric. Individuals with generalized epilepsy typically show generalized spike-wave or generalized paroxysmal fast activity on electroencephalogram (EEG).
- **Focal epilepsy**: The term focal has replaced partial to describe epilepsy associated with seizures that are inferred from clinical or EEG data to originate in networks limited to one hemisphere. Focal seizures may arise from either subcortical structures or neocortex. Most individuals with focal epilepsy show focal multifocal discharges on interictal EEG.
- **Generalized and focal epilepsy**: This term should be used for epilepsies that have both generalized and focal seizures. This category includes several epilepsy syndromes, particularly those with onset in early childhood, such Dravet syndrome or Lennox-Gastaut syndrome, but may also be relevant for epilepsies associated with diffuse or focal structural, genetic or metabolic etiologies. The interictal EEG may show both generalized and focal/multifocal discharges, or epileptiform discharges may be absent.
- **Unknown if generalized or focal epilepsy**: This term is used for epilepsies with seizures in which it cannot be clearly determined whether onset is focal or generalized. A key example is epileptic spasms, which may appear generalized despite being caused by a focal lesion. The term unknown should also be used in an individual who presents with a generalized tonic-clonic seizure and normal examination but whose EEG and neuroimaging is either noninformative or unavailable.

Vagus nerve stimulation (VNS) was originally approved for the treatment of medically refractory epilepsy. Significant advances have been made since then in the surgical and

medical treatment of epilepsy, and new, more recently approved medications are available. Despite these advances, however, 25% to 50% of patients with epilepsy experience breakthrough seizures or suffer from debilitating adverse effects of anti-seizure medications. VNS is typically used when a patient has had unsuccessful medical therapy, been intolerant of medical therapy, or has failed resective surgery.

While the mechanisms for the therapeutic effects VNS are not fully understood, the basic premise of VNS in the treatment of various conditions is that vagal visceral afferents (nerves that convey impulses from sense organs and other receptors to the brain or spinal cord) have diffuse central nervous system projection, and the activation of these pathways has a widespread effect upon neuronal excitability. An electrical stimulus is applied to axons of the vagus nerve, which have their cell bodies in the nodose and junctional ganglia and synapse on the nucleus of the solitary tract in the brainstem. From the solitary tract nucleus, vagal afferent pathways project to multiple areas of the brain. VNS may also stimulate vagal efferent pathways that innervate the heart, vocal cords, and other laryngeal and pharyngeal muscles, and provider parasympathetic innervation to the gastrointestinal tract. Adverse effects of VNS therapy include headache, neck pain, cough and voice alterations.

Some of the benefits of using VNS may include less severe or shorter seizures, a reduction in seizure frequency, improved recovery periods after seizures, and a lessening of seizure clusters. Individuals undergoing VNS must be aware that seizure control improves over time, and that although VNS may reduce the frequency and magnitude of seizure activity, the need remains for ongoing, concurrent, anti-seizure medical regimen.

Vagus nerve stimulation (VNS) is an implantable, programmable electronic pulse generator that delivers stimulation to the left vagus nerve at the carotid sheath. Surgery for implantation of a vagus nerve stimulator involves implantation of the pulse generator in the infraclavicular region and wrapping 2 spiral electrodes around the left vagus nerve within the carotid sheath. The programmable stimulator may be programmed in advance to stimulate at regular intervals or on demand by patients or family by placing a magnet against the sub clavicular implant site.

The stimulator is generally activated two to four weeks after implantation, although in some cases it may be activated in the operating room at the time of implantation. The physician programs the stimulator with a small hand-held computer, programming software, and a programming wand. The strength and duration of the electrical impulses are programmed. The amount of stimulation varies by case but is usually initiated at a low level and slowly increased to a suitable level for the individual.

Patients are provided with a handheld magnet to control the stimulator at home (which must be activated by the physician to magnet mode). When the magnet is placed over the pulse generator site and then moved away, extra stimulation is delivered, regardless of the treatment schedule. Holding the magnet over the pulse generator will turn the stimulation off. Removing it will resume the stimulation cycle. This can be done by the patient, family members, friends, or caregivers.

Treatment Resistant Seizures

Clinical Context and Purpose
The purpose of implantable vagus nerve stimulation (VNS) in individuals with seizures refractory to medical therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies.

Populations
The relevant population of interest is individuals with medically refractory seizures.

Intervention
The therapy being considered is implantable vagus nerve stimulation (VNS). Surgically implanted VNS devices consist of an implantable, programmable electronic pulse generator that delivers stimulation to the left vagus nerve at the carotid sheath. The pulse generator is connected to the vagus nerve via a bipolar electrical lead. Surgery for implantation of a vagal nerve stimulator involves implantation of the pulse generator in the infraclavicular region and wrapping 2 spiral electrodes around the left vagus nerve within the carotid sheath. The programmable stimulator may be programmed in advance to stimulate at regular intervals or on demand by patients or a family member by placing a magnet against the sub clavicular implant site.

Comparators
VNS is typically used when an individual has had unsuccessful medical standard therapy, or have been intolerant of medical standard therapy or has failed resective surgery.

For the treatment of refractory seizures, the following practices are currently being used: resective surgery, additional trial of conventional antiepileptic drugs and/or ketogenic diet.

Outcomes
For treatment of refractory epilepsy, the outcomes of interest are seizure frequency and severity, reduction in seizure frequency by >50%, quality of life and functional outcomes, cognitive function, mediation use and treatment-related morbidity.

Review of Evidence

Systematic Reviews
Reports on the use of vagus nerve stimulation (VNS) to treat medication-resistant seizure disorders date to the 1990s and were coincident with preapproval and early post approval study of the device.

Characteristics of Systematic Reviews of Implantable VNS for Epilepsy

Study	Dates	Studies	Participants	N (Range)	Design	Duration
Panebianco et al. (2015)	Up to 2015	5	Adults or children with drug-resistant partial seizures not eligible for surgery or who failed surgery	439 (22 to 198)	RCT	12 to 20 weeks
Englot et al. (2011)	Up to 2010	15	Adults or children with medically refractory epilepsy	955 (16 to 196)	RCT or prospective observational study	3 months to 5 years

RCT: randomized controlled trial; VNS: vagus nerve stimulation.

Results of Systematic Reviews for Randomized Controlled Trials of Implantable VNS for Epilepsy

Study	50% of Greater Reduction in Seizure Frequency	VNS Treatment Withdrawal	Voice Alteration or Cough	Cough	Dyspnea
Panebianco et al. (2015)					
Total N	373	375	334	334	312
Pooled effect (95% CI)	1.73 (1.13 to 2.64)	2.56 (0.51 to 12.71)	2.17 (1.49 to 3.17)	1.09 (0.74 to 1.62)	2.45 (1.07 to 5.60)
I2 (p[a])	18% (p=.30)	0% (p=.74)	32% (p=.23)	0% (p=.54)	0% (p=.77)

CI: confidence interval; RCT: randomized controlled trial; VNS: vagus nerve stimulation.
[a] p for heterogeneity

Randomized Controlled Trials

Five randomized controlled trials (RCTs) (N=439) have evaluated vagus nerve stimulation (VNS). Four trials compared high-frequency VNS that was thought to be therapeutic versus low-frequency VNS at levels that were thought to be sub-therapeutic. One trial compared rapid versus medium versus slow cycle VNS. Characteristics and results of the trials are shown below in tables.

Characteristics of Double-Blind Randomized Controlled Trials of VNS for Epilepsy

Study: Trial	Dates	Participants	Interventions	
			Active	Comparator
Klinkenberg et al (2012)	NR	Children with medically refractory epilepsy not eligible for epilepsy surgery (race or ethnicity not reported)	n=21 High output	n=20 Low output
DeGiorgio et al (2005)	NR	Patients ages 12 years and older, 1 or more antiepileptic medications and at least 1 seizure/30 days with alteration of consciousness (race or ethnicity not reported)	n=19 Rapid cycle N=19 Med cycle	n=23 Slow cycle
Handforth et al (1998)	1995 to 1996	Patients with 6+ partial-onset seizures over 30 days including complex partial or secondarily generalized seizures (86.4% white, 8.6% Hispanic/Latino,	n=95 High stimulation	n=103 Low stimulation

		5% race/ethnicity not reported)		
Ben-Menchem et al/VNS Study Group (1994, 1995)	1991	Patients with refractory partial (simple or complex) seizures Mean age, 35 years (range 14 to 57) (race or ethnicity not reported)	n=54 High stimulation	n=60 Low stimulation
Michael et al (1993)	NR	Patients with refractory partial seizures (race or ethnicity not reported)	n=10 High stimulation	n=12 Low stimulation

NR: not reported; RCT: randomized controlled trial; VNS: vagus nerve stimulation.

The trials generally included people with drug-resistant partial epilepsy with VNS as an add-on treatment. The blinded treatment phase ranged from 12 to 20 weeks in the 5 trials. Four trials reported the outcome of response (50% or greater reduction in seizure frequency) and the risk ratio ranged from 1.49 to 8.27 in the 3 trials that favored high-frequency VNS; the risk ratio was statistically significantly different from the null in 1 trial. One trial reported a risk ratio that did not favor high-frequency VNS for the response outcome but was not statistically significant.

Results of Double-Blind Randomized Controlled Trials for VNS for Epilepsy

Study	**50% or Greater Reduction in Seizure Frequency (%)**	**Change in Seizure Frequency**	**Quality of Life**	**Functional Outcomes**
Klinkenberg et al (2012)				
N	41	41	NR	NR

High stimulation	14%	+23%		
Low Stimulation	20%	-9%		
Treatment Effect (95% CI)	RR=0.71 (0.18 to 2.80)	p=.61		
DeGiorgio et al (2005)				
N	42	NR	NR	NR
Rapid cycle	32%	-26%		
Slow cycle	26%	-29%		
Treatment Effect (95% CI)	NR	NR		
Handforth et al (1998)				Global evaluation scores of patient well-being with visual analog scale by blinded interviewer at visits 7-9, mean
N	196	196	NR	
High stimulation	23%	-28%	NR	
Low Stimulation	16%	-15%	NR	
Treatment Effect (95% CI)	RR=1.49 (0.84 to 2.66)	p=.04	Difference=4.0 mm (0.6 to 7.4); p=.02	
Ben-Menchem/VNS				

Study Group (1994, 1995)				
N	114	67	NR	NR
High stimulation	31%	-31%		
Low Stimulation	13%	-11%		
Treatment Effect (95% CI)	RR=2.36 (1.11 to 5.03)	Difference=-20% (NR); p=.03		
Michael et al (1993)				
N	22	NR	NR	
High stimulation	30%			
Low Stimulation	0%			
Treatment Effect (95% CI)	RR=8.27 (0.48 to 143.35)			

CI: confidence interval; NR=not reported; RCT: randomized controlled trial; RR=Risk ratio; VNS: vagus nerve stimulation.

Ryvlin et. al. (2014) reported on an RCT on long-term quality of life outcomes for 112 patients with medication-resistant focal seizures, which supported the beneficial effects of VNS for this group.

Observational Studies

Resective surgery is a less attractive therapeutic option for individuals with generalized treatment-resistant seizures that may be multifocal or involve an eloquent area. VNS has been evaluated as an alternative to disconnection procedures such as surgical division of the corpus callosum. The evidence for the efficacy of VNS for generalized seizures in adults is primarily from observational data, including registries and small cohort studies. Englot et al (2016) examined freedom from seizure rates and predictors across 5554 patients enrolled in the VNS Therapy Patient Outcomes Registry. The registry was established in 1999, after the 1997 U.S. Food and Drug Administration (FDA) approval of VNS, and is maintained by the manufacturer of the device, Cyberonics. Data were prospectively collected by 1285 prescribing physicians from 978 centers (911 in the United States and Canada and 67 internationally) at patients' preoperative baselines and

various intervals during therapy. During active data collection, participation in the registry included approximately 18% of all implanted VNS devices. The database was queried in January 2015, and all seizure outcomes reported with the 0- to 4-, 4- to 12-, 12- to 24-, and 24- to 48-month time ranges after VNS device implantation were extracted and compared with patient preoperative baseline. Available information was tracked at each time point of data submission for the following outcomes: patient demographics, epilepsy etiology and syndrome, historical seizure types and frequencies, quality of life, physician global assessment, current antiepileptic drugs, medication changes, malfunctions, battery changes, and changes in therapy. At each observation point, responders were defined as having a 50% or greater decrease in seizure frequency compared with baseline and nonresponders as less than a 50% decrease. A localized epilepsy syndrome such as partial-onset seizures was recorded in 59% of the registry participants, generalized epilepsy in 27%, and 11% had a syndromic etiology (e.g., Lennox-Gastaut). The outcomes for the approximately 1500 registry enrollees with generalized seizures are summarized in below Table. These rates did not differ statistically from participants with predominantly partial seizures.

Summary of VNS Registry Outcomes

Generalized Seizures	Responder Rate, %[a]	Seizure Freedom Rate, %
0-4 months	50	7
4-12 months	55	8
12-24 months	55	8
24-48 months	≈60[b]	≈9[a]

VNS: vagus nerve stimulation;
[a] Responder rate: ≥50% decrease in seizure frequency;
[b] Approximation based on publication Figure 1 and narrative.

Garcia-Navarrete et al. (2013) evaluated outcomes after 18 months of follow-up for a prospective cohort of 43 patients with medication-resistant epilepsy who underwent VNS implantation. Subjects' seizure types were heterogeneous, but 52% had generalized epilepsy. Pharmacotherapy was unchanged during the study. Twenty-seven (63%) subjects were described as "responders," defined as having a 50% or greater reduction in seizure frequency compared with the year before VNS implantation. The difference in reduction of seizure frequency was not statistically significant between subjects with generalized and focal epilepsy.

The evidence for VNS for pediatric seizures consists of a variety of small noncomparator trials, prospective observational studies, and retrospective case series. As in the adult studies, there is heterogeneity of seizure etiologies: mixed, syndromic, and idiopathic; there is also generalized and limited information on concomitant antiepileptic drug requirement. Some studies have defined pediatric patients as less than 12 years of age and others have defined them as less than 18 years and may have included patients as young

as 2 to 3 years of age. Study subpopulations may have had prior failed resective surgery. Complete freedom from seizures is the exception, and the primary reported endpoint is 50% or more reduction in seizure frequency, determined over varying lengths of follow-up. There is an overlap of authors for multiple studies suggesting utilization of VNS in specialized clinical care environments. Multiple studies have some form of innovator device company sponsorship.

Summary of VNS Pediatric Studies

Author (Year)	Study Type	Sample	Seizure Disorder Type	Duration of FU	SFR ≥50% or Median Reduction, n (%)[a]	Notes
Yu et al (2014)	Retrospective case review	69/252[f]	Mixed	12 mo	28 (40.6)	Age: <12 y=28
Terra et al (2014)	Retrospective case-control[d]	36	Mixed	3-y review	VNS group: 20 (55.4)	Age: <18 y Difference from baseline seizure frequency[e]
Healy et al (2013)	Retrospective case review	16	Unknown	3-y review	9 (56)	Age: <12 y
Cukiert et al (2013)	Case series	24	LGS	24 mo	NR[c]	Age: <12 y
Klinkenberg et al (2012)	RCT[b]	41	Mixed	19 wk	High-stim: 3/21 (14.2) Low-stim: 4/20 (20)	Age range: 3-17 y
You et al (2007)	Prospective OBS	28	Mixed	31.4 mo (mean)	15 (53.6)	Age range: 2-17 y
Frost et al (2001)	Retrospective case review	50	LGS	6 mo	50 (57.9)[a]	Age: 13 y (median)

Patwardhan et al (2000)	Case series	38	Mixed	12 mo (median)	26 (68)	Age: 11 mo to 16 y
Murphy et al (1999)	Prospective OBS	60	Mixed	18 mo	46 (42)[a]	Age: 26% <12 y
Hornig et al (1997)	Case series	19	Mixed	2-30 mo	10 (53)	Prior failed resective surgery: n=3

FU: follow-up; LGS: Lennox-Gastaut syndrome; NR: not reported; OBS: observational; RCT: randomized controlled trial; SD: standard deviation; SFR: seizure frequency reduction; VNS: vagus nerve stimulation.
a Median reduction in total seizure frequency.
b RCT comparing high- (n=21) with low-stimulation (n=20) VNS.
c Seizure reduction not reported but 10 (41.6%) experienced transient seizure frequency worsening.
d Age-matched 31 VNS with 72 non-VNS controls.
e Baseline seizure frequency; VNS: 346.64 (SD=134.11) versus control group: 83.63 (SD=41.43).
f Sixty-nine of 252 of identified cases had evaluable pre- and post-implantation data.

Section Summary
The evidence on the efficacy of vagus nerve stimulation (VNS) for treatment of medically refractory seizures consists of randomized controlled trials (RCTs), meta-analyses and numerous uncontrolled studies. RCTs and meta-analyses of RCTs have reported a significant reduction in seizure frequency with VNS for patients with partial-onset seizures. The uncontrolled studies and case series have consistently reported reductions of clinical significance, defined as a 50% or more reduction in seizure frequency in both adults and children over almost 2 decades of publications. Interpretation of all outcomes and results were limited by the variety of comparators (when used), variability in length of follow-up, limited published data on antiepileptic medication requirements, mixed seizure etiologies, and history of prior failed resective surgery. There is an overlap of authors across multiple studies, suggesting utilization of VNS in specialized clinical care environments. Multiple studies have some form of innovator device company sponsorship.

Treatment Resistant Depression

Clinical Context and Therapy Purpose
The purpose of implantable vagus nerve stimulation (VNS) in individuals with treatment-resistant depression is to provide a treatment option that is an alternative to or an improvement on existing therapies.

Populations
The relevant population of interest is individuals with treatment-resistant depression.

Interventions
The therapy being considered is implantable VNS.

Surgically implanted VNS devices consist of an implantable, programmable electronic pulse generator that delivers stimulation to the left vagus nerve at the carotid sheath. The pulse generator is connected to the vagus nerve via a bipolar electrical lead. Surgery for implantation of a vagal nerve stimulator involves implantation of the pulse generator in the infraclavicular region and wrapping 2 spiral electrodes around the left vagus nerve within the carotid sheath. The programmable stimulator may be programmed in advance to stimulate at regular intervals or on demand by patients or families by placing a magnet against the subclavicular implant site.

Comparators
VNS is typically used when a patient has had unsuccessful medical standard therapy or, is intolerant of medical standard therapy, or had failed resective surgery.

There are treatment modalities for which there is substantial evidence of effectiveness in the treatment of a major depressive episode (MDE): pharmacotherapy with antidepressant drugs (ADDs), specific forms of psychotherapy (e.g., cognitive behavior and interpersonal therapy), transcranial magnetic stimulation (TMS) and electroconvulsive therapy (ECT). ADDs are the usual first-line treatment for depression. Clinical trials have demonstrated efficacy for several pharmacologic classes of ADDs. Physicians usually reserve ECT for treatment-resistant cases or when they determine a rapid response to treatment is desirable. For those patients who do not respond to initial antidepressant treatment, physicians generally use one or more of the following strategies: 1) switching to an alternative first line ADD; 2) switching to a second line ADD; 3) adding psychotherapy, a second ADD, or an augmentation agent (not generally considered to have significant antidepressant activity when administered alone). Additional options for treatment-resistant patients, especially for patients who fail on the above alternatives, include monoamine oxidase inhibitors and ECT. For treatment-resistant cases that exhibit a marked seasonal pattern, adding phototherapy to pharmacotherapy may also be an option. VNS has been proposed as an adjunct therapy in patients with major depressive disorder.

Outcomes
For treatment-resistant depression, the outcomes of interest are depression symptoms as measured by the Montgomery-Asberg Depression Rating Scale or Hamilton Depression Rating Scale, response and remission, global impression of change, suicide, quality of life and functional outcomes, and treatment-related morbidity. Relief of depression symptoms can be assessed by any one of many different depression symptom rating scales. A 50% reduction from baseline score is considered to be a reasonable measure of treatment response. Improvement in depression symptoms may allow reduction of pharmacologic therapy for depression, with a reduction in adverse events related to that form of treatment. In the studies evaluating VNS therapy, the 4 most common instruments used were the Hamilton Rating Scale for Depression, Clinical Global Impression, Montgomery and Asberg Depression Rating Scale, and the Inventory of Depressive Symptomatology (IDS)

For treatment-resistant depression, data on outcomes related to depression symptoms are needed over the short-term (2 to 6 months) and the long-term (1 to 2 years).

Review of Evidence

Systematic Reviews

Bottomley et al (2020) reported results of a systematic review and meta-analysis of 2 RCTs (Rush et al [2005] and Aaronson et al [2013]), 16 single-arm and 4 nonrandomized comparative studies. The meta-analysis calculated overall pooled effect estimates for VNS and treatment-as-usual groups, respectively, but did not perform quantitative analysis of comparative treatment effects. Thus, this meta-analysis provides insufficient evidence to permit comparisons between VNS and the control groups.

Randomized Controlled Trials

Aaronson et al (2013) reported on results from an active-controlled trial in which 331 patients with a history of chronic or recurrent bipolar disorder or major depressive disorder, with a current diagnosis of a major depressive episode, were randomized to 1 of 3 VNS current doses (high, medium, low). Patients had a history of failure to respond to at least 4 adequate dose/duration of antidepressant treatment trials from at least 2 different treatment categories. After 22 weeks, the current dose could be adjusted in any of the groups. At follow-up visits at weeks 10, 14, 18, and 22 after enrollment, there were no statistically significant differences between the dose groups for the study's primary outcome, change in IDS score from baseline. However, mean IDS scores improved significantly for each group from baseline to the 22-week follow-up. At 50-week follow-up, there were no significant differences between the treatment dose groups for any of the depression scores used. Most patients completed the study; however, there was a high rate of reported adverse events, including voice alteration in 72.2%, dyspnea in 32.3%, and pain in 31.7%. Interpretation of the IDS improvement over time is limited by the lack of a no-treatment control group. Approximately 20% of the patients included had a history of bipolar disorder; as such, the results might not be representative of most patients with treatment-resistant unipolar depression.

Rush et al (2005) reported results of a 10-week, blinded RCT comparing adjunctive VNS with sham (implanted but inactivated VNS) in 235 outpatients with nonpsychotic major depressive disorder or nonpsychotic, depressed phase, bipolar disorder (D-02). The patients were treatment-resistant defined as those who had not responded adequately to between 2 and 6 research-qualified medication trials for the current episode of depression. The primary outcome was response rates (50% or more reduction from baseline on the Hamilton Rating Scale for Depression). There was not a statistically significant difference in response rates at 10 weeks in VNS versus sham (15% vs. 10%; p=.25). The Inventory for Depressive Symptomatology Systems Review score was considered a secondary outcome and showed a difference that was statistically significant in favor of VNS (17.4%) compared with sham treatment (7.5%; p=.04).

Prospective Observational Studies
The observational study that compared patients participating in the RCT with patients in a separately recruited control group (D-04 vs. D-02, respectively) evaluated VNS therapy out to 1 year and showed a statistically significant difference in the rate of change of depression score.[9] However, issues such as unmeasured differences among patients, nonconcurrent controls, differences in sites of care between VNS therapy patients and controls, and differences in concomitant therapy changes raise concern about this observational study. Analyses performed on subsets of patients cared for in the same sites, and censoring observations after treatment changes, generally showed diminished differences in apparent treatment effectiveness of VNS and almost no statistically significant differences. Patient selection for the randomized trial and the observational comparison trial may be of concern. VNS is intended for treatment-refractory depression, but the entry criteria of failure of 2 drugs and a 6-week trial of therapy might not be a strict enough definition of treatment resistance. Treatment-refractory depression should be defined by thorough psychiatric evaluation and comprehensive management. It is important to note that patients with clinically significant suicide risk were excluded from all VNS studies. Given these concerns about the quality of the observational data, these results did not provide strong evidence for the effectiveness of VNS therapy.

McAllister-Williams et al (2020) reported on results of a subgroup of 156 participants with treatment-resistant bipolar depression from the above-described FDA-required post-marketing surveillance study (Aaronson et al [2017]). Compared to the overall population in the primary study, cumulative first-time response rates were similar in this bipolar depression subgroup (63% vs. 39%; p not reported). Median time-to-initial response was not significantly different between groups (13.7 vs. 42.1 months; Hazard Ratio [HR]=1.7; 95% CI, 1 to 2.7). Median time-to-relapse from initial response in the first year was also not significantly different between groups (15.2 vs. 7.6 months; HR=0.7; 95% CI, 0.3 to 1.4). Based on MADRS item 10, the mean reduction in suicidality score across the study visits was reportedly significantly greater in the VNS group than in the no VNS group ($p<.001$ as per F-test). However, the validity of this finding is unclear as by 60 months, it excluded data from an unacceptably high (n=100, 64%) and imbalanced (59% in VNS group vs. 73% in no VNS group) number of patients with unavailable suicidality data. It was additionally subject to the same important limitations as described above for the primary study.

In 2017, Aaronson et. al. reported long-term outcomes from the five-year post-marketing surveillance study of individuals with treatment resistance depression treated with VNS or "treatment as usual." The prospective, open-label, nonrandomized, observational registry study, was conducted at 61 U.S. sites. The study included a total of 795 patients who were experiencing a major depressive episode (unipolar or bipolar depression) of at least two years' duration or had three or more depressive episodes (including the current episode), and who had failed four or more depression treatments (including ECT). Patients with a history of psychosis or rapid-cycling bipolar disorder were excluded. The primary efficacy measure was response rate, defined as a decrease of ≥50% in baseline Montgomery Åsberg Depression Rating Scale (MADRS) score at any post baseline visit

during the five-year study. Secondary efficacy measures included remission. Patients had chronic moderate to severe depression at baseline (the mean MADRS score was 29.3 [SD=6.9] for the treatment-as-usual group and 33.1 [SD=7.0] for the adjunctive VNS group). The registry results indicate that the adjunctive VNS group had better clinical outcomes than the treatment- as-usual group, including a significantly higher five-year cumulative response rate (67.6% compared with 40.9%) and a significantly higher remission rate (cumulative first-time remitters, 43.3% compared with 25.7%). A sub-analysis demonstrated that among patients with a history of response to ECT, those in the adjunctive VNS group had a significantly higher five-year cumulative response rate than those in the treatment-as-usual group (71.3% compared with 56.9%). A similar significant response differential was observed among ECT nonresponders (59.6% compared with 34.1%). The naturalistic, observational study design did not allow for random assignment of participants to treatment groups; thus, participants were not blinded to treatment. A significant number of participants in both groups withdrew early from the study. Of the 358 patients (45%) who withdrew early, 195 were from the VNS arm (40%) and 163 were from the treatment-as-usual arm (54%). The reasons for early withdrawal were similar between the treatment arms. The significantly higher treatment response rate observed in the VNS arm may represent a treatment effect, as participants with an implanted device may have had a higher expectation of therapeutic improvement.

Section Summary
Randomized controlled trials (RCTs) evaluating the efficacy of implanted vagus nerve stimulation (VNS) for treatment-resistant depression compared to sham and 1 RCT comparing therapeutic to low-dose implanted VNS. The sham-controlled trials reported only short-term results and found no significant improvement in the primary outcome with VNS. The low-dose VNS controlled trial reported no statistically significant differences between the dose groups for change in depression symptom score from baseline. Other available studies, which include nonrandomized comparative studies and case series, are limited by relatively small sample sizes and the potential for selection and confounding biases; the case series are further limited by the lack of control groups. Given the limitations of this literature, combined with the lack of substantial new clinical trials, the scientific evidence is considered to be insufficient to permit conclusions on the effect of this technology on major depression.

Treatment of Chronic Heart Failure

Clinical Context and Therapy Purpose
The purpose of implantable vagus nerve stimulation (VNS) in individuals with chronic heart failure is to provide a treatment option that is an alternative to or an improvement on existing therapies.

Populations
The relevant population of interest is individuals with chronic heart failure.

Interventions
The therapy being considered is implantable VNS.

Surgically implanted VNS devices consist of an implantable, programmable electronic pulse generator that delivers stimulation to the left vagus nerve at the carotid sheath. The pulse generator is connected to the vagus nerve via a bipolar electrical lead. Surgery for implantation of a vagal nerve stimulator involves implantation of the pulse generator in the infraclavicular region and wrapping 2 spiral electrodes around the left vagus nerve within the carotid sheath. The programmable stimulator may be programmed in advance to stimulate at regular intervals or on demand by patients or families by placing a magnet against the subclavicular implant site.

Comparators
Comparators of interest include medication management and physical rehabilitation. VNS is typically used when a patient has had unsuccessful medical standard therapy or is intolerant of medical standard therapy.

Outcomes
The general outcomes of interest are symptoms, change in disease status, and functional outcomes.

Follow-up of months to years is of interest to monitor outcomes.

Review of Evidence
Sant'Anna et al (2021) conducted a systematic review and meta-analysis on clinical trials comparing VNS with medical therapy for the management of chronic heart failure with reduced ejection fraction. Four RCTs and 3 prospective studies were identified (N=1263). Only data from the 4 RCTs were included in the meta-analysis. The certainty of the evidence based on GRADE characteristics was reported as high for all outcomes. Characteristics of the systematic review are described in the table below. The meta-analysis found significant improvements in New York Heart Association functional class, quality of life, 6-minute walk test, and N-terminal-pro brain natriuretic peptide levels in patients treated with VNS compared to sham, see below table.

Characteristics of Systematic Reviews of Implantable VNS for Chronic Heart Failure

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Sant'Anna et al (2021)	1994 to 2020	**7**	Adults with heart failure with reduced ejection fraction	1263 (95 to 707)	4 RCTs, 3 prospective studies	median follow-up was 6 months (range: 6

						to 16 months)

RCT: randomized controlled trial; VNS: vagus nerve stimulation

Results of Systematic Reviews of Randomized Controlled Trials of Implantable VNS for Chronic Heart Failure

Study	Improvement in NYHA Functional Class	Quality of Life	6-Minute Walk Test	NT-proBNP Levels	Mortality
Sant'Anna et al (2021)					
Total N	969 (4 RCTs)	450 (3 RCTs)	728 (3 RCTs)	445 (3 RCTs)	1206 (4 RCTs)
Pooled effect (95% CI)	OR, 2.72; (2.07 to 3.57); p<.0001	MD, -14.18 (-18.09 to -10.28)	MD, 55.46 meters (39.11 to 71.81)	MD, -144.25 (-238.31 to -50.18)	OR, 1.24 (0.82 to 1.89)
I^2 (p)	37% (p<.0001)	49% (p<.0001)	0% (p<.0001)	65% (p=.003)	0% (p=.43)

CI: confidence interval; MD: mean difference; NNT: number needed to treat; NT-proBNP: N-terminal-pro brain natriuretic peptide; NYHA: New York Heart Association; OR: odds ratio; RCT: randomized controlled trial; VNS: vagus nerve stimulation
[a]Assessed by the Minnesota Living with Heart Failure Questionnaire (MLwHFQ)

Case Series

Vagus nerve stimulation (VNS) has been investigated for the treatment of chronic heart failure in case series. A 2011 phase 2 case series of VNS therapy for chronic heart failure reported improvements in New York Heart Association class quality of life, 6-minute walk test, and left ventricular (LV) ejection fraction.[40,] The Autonomic Neural Regulation Therapy to Enhance Myocardial Function in Heart Failure With Preserved Ejection Fraction (ANTHEM-HF) trial (2014) is another case series, but in it, patients were randomized to right- or left-sided vagus nerve implantation (but without a control group). Overall, from baseline to 6-month follow-up, a number of measures were improved: LV ejection fraction improved by 4.5% (95% CI, 2.4% to 6.6%); LV end-systolic volume improved by -4.1 mL (95% CI, -9.0 to 0.8 mL); LV end-diastolic diameter improved by -1.7 mm (95% CI, -2.8 to -0.7 mm); heart rate variability improved by 17 ms (95% CI, 6.5 to 28 ms); and 6-minute walk distance improved by 56 meters (95% CI, 37 to 75 meters). A follow-up analysis to ANTHEM-HF by Nearing et al (2021) evaluated outcomes of VNS at 12, 24, and 36 months.[49,] They found that LV ejection fraction improved by 18.7% (p=.008), 19.3% (p=.04), and 34.4% (p=.009) at 12,

24, and 36 months, respectively, with high-intensity VNS. Individuals with low-intensity VNS only had significant improvement in LV ejection fraction at 24 months (12.3%; p=.04).

Section Summary
The evidence on vagus nerve stimulation (VNS) for treatment of chronic heart failure consists of a systematic review including 4 randomized controlled trials (RCTs) and 2 uncontrolled studies. A meta-analysis of 4 RCTs found significant improvements in New York Heart Association functional class, quality of life, 6-minute walk test, and N-terminal-pro brain natriuretic peptide levels in patients treated with VNS compared to sham. The uncontrolled studies consistently reported improvements on a variety of measures, including LV function, 6-minute walk test and quality of life. However, lack of a no-VNS comparator group precludes drawing conclusions based on findings from the uncontrolled studies.

Treatment of Upper-Limb Impairment due to Stroke

Clinical Context and Therapy Purpose
The purpose of implantable vagus nerve stimulation (VNS) in individuals with upper-limb impairment due to stroke is to provide a treatment option that is an alternative to or an improvement on existing therapies.

Populations
The relevant population of interest is individuals with upper-limb impairment due to stroke.

Interventions
The therapy being considered is implantable VNS.

Surgically implanted VNS devices consist of an implantable, programmable electronic pulse generator that delivers stimulation to the left vagus nerve at the carotid sheath. The pulse generator is connected to the vagus nerve via a bipolar electrical lead. Surgery for implantation of a vagal nerve stimulator involves implantation of the pulse generator in the infraclavicular region and wrapping 2 spiral electrodes around the left vagus nerve within the carotid sheath. The programmable stimulator may be programmed in advance to stimulate at regular intervals or on demand by patients or families by placing a magnet against the subclavicular implant site.

Comparators
Comparators of interest include medication management and physical rehabilitation. VNS is typically used when a patient has had unsuccessful medical standard therapy or is intolerant of medical standard therapy.

Outcomes
The general outcomes of interest are symptoms, change in disease status, and functional outcomes.

Follow-up of weeks to months is of interest to monitor outcomes.

Review of Evidence
Dawson et al (2016) conducted a randomized pilot trial of VNS in patients with upper-limb dysfunction after ischemic stroke. Twenty-one subjects were randomized to VNS plus rehabilitation or rehabilitation alone. The mean change in the outcome as assessed by a functional assessment score was +8.7 in the VNS group and +3.0 in the control group (p=.064). Six patients in the VNS group achieved a clinically meaningful response and 4 in the control group (p=.17). A similar RCT with a larger patient population was conducted by the same study group in 2021 (Dawson et al). Patients with upper-limb dysfunction after ischemic stroke (N=106) were randomly assigned 1:1 to either VNS plus rehabilitation or rehabilitation with sham stimulation. The Fugl-Meyer Assessment-Upper Extremity score increased by 5 points in the VNS group and 2.4 points in the control group (between-group difference, 2.6; 95% CI, 1.0 to 4.2; p=.0014). Ninety days after in-clinic therapy, a clinically meaningful response was achieved in 23 (47%) of 53 patients in the VNS group versus 13 (24%) of 55 patients in the control group (between-group difference, 24%; 95% CI, 6 to 41; p=.0098). There was 1 adverse event of vocal cord paresis related to surgery in the control group.

Kimberley et al (2019) reported results of a randomized, pilot sham controlled RCT in 17 patients (VNS =8 and sham VNS, n=9) with arm weakness after ischemic stroke. The mean Fugl-Meyer assessment–upper extremity scores increased by 7.6 with VNS versus 5.3 points with sham at day 1 (Difference=2.3 points; 95% CI, −1.8 to 6.4; p=.20) and 9.5 points with VNS versus 3.8 with sham at day 90 (Difference=5.7 points; 95% CI, −1.4 to 11.5; p=.055). A Fugl-Meyer assessment–upper extremity change ≥6 points was defined as response; the response rate at day 90 was 88% with VNS versus 33% with sham (p<.05). There were 3 serious adverse events related to surgery: wound infection, shortness of breath and dysphagia, and hoarseness because of vocal cord palsy.

Section Summary
The evidence on vagus nerve stimulation (VNS) for treatment of upper-limb impairment due to stroke consists of 3 small randomized controlled trials (RCTs). Two RCTs compared VNS plus rehabilitation to rehabilitation alone; 1 failed to show significant improvements for the VNS group on response and function outcomes, but the other, which had a larger patient population, found a significant difference in response and function outcomes. The other RCT compared VNS to sham and found that although VNS significantly improved response rate, there were 3 serious adverse events related to surgery.

Vagus Nerve Stimulation for Other Neurologic Conditions (Essential Tremor, Headache, Fibromyalgia, Tinnitus and Autism)

Clinical Context and Therapy Purpose
The purpose of vagus nerve stimulation (VNS) in individuals with other neurologic conditions (e.g., essential tremor, headache, fibromyalgia, tinnitus, and autism) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

Populations
The relevant population of interest is individuals with other neurologic conditions (e.g., essential tremor, headache, fibromyalgia, tinnitus, and autism).

Interventions
The therapy being considered is implantable VNS.

Surgically implanted VNS devices consist of an implantable, programmable electronic pulse generator that delivers stimulation to the left vagus nerve at the carotid sheath. The pulse generator is connected to the vagus nerve via a bipolar electrical lead. Surgery for implantation of a vagal nerve stimulator involves implantation of the pulse generator in the infraclavicular region and wrapping 2 spiral electrodes around the left vagus nerve within the carotid sheath. The programmable stimulator may be programmed in advance to stimulate at regular intervals or on demand by patients or families by placing a magnet against the subclavicular implant site.

Comparators
Comparators of interest include medication and behavioral therapy. VNS is typically used when a patient has had unsuccessful medical standard therapy or is intolerant of medical standard therapy.

Outcomes
The general outcomes of interest are symptoms, change in disease status, and functional outcomes.

Review of Evidence
Vagus nerve stimulation (VNS) has been investigated with small pilot studies or studies evaluating the mechanism of disease for several conditions. These conditions include essential tremor, fibromyalgia, and tinnitus. The utility of VNS added to behavioral management of autism and autism spectrum disorders has been posited, but there are no RCTs. None of these studies are sufficient to draw conclusions on the effect of VNS on these conditions.

Section Summary
Other conditions (essential tremor, fibromyalgia, tinnitus, autism) have only been investigated with case series, which are not sufficient to draw conclusions on the effect of VNS.

Prevention of Cluster Headaches

Clinical Context and Therapy Purpose
The purpose of noninvasive or transcutaneous vagus nerve stimulation (nVNS or tVNS) is to non-invasively apply low-voltage electrical currents to stimulate the cervical branch of the vagus nerve. NVNS has been tested primarily in the setting of headache. NVNS has been proposed as an intervention to reduce the frequency of attacks for cluster headaches as an adjunct to standard care.

Populations
The relevant population of interest is individuals with cluster headache, using n VNS for prevention. The International Headache Society's International Classification of Headache Disorders classifies types of primary and secondary headaches.[56,] A summary of cluster headache based on the International Classification of Headache Disorders criteria is below.

Cluster headaches are primary headaches classified as trigeminal autonomic cephalalgias that can be either episodic or chronic. The diagnostic criteria for cluster headaches states that these are attacks of severe, unilateral orbital, supraorbital, and/or temporal pain that lasts 15 to 180 minutes and occurs from once every other day to 8 times a day and further requires for the patient to have had at least 5 such attacks with at least 1 of the following symptoms or signs, ipsilateral to the headache: conjunctival injection and/or lacrimation; nasal congestion and/or rhinorrhea; eyelid edema; forehead and facial sweating; miosis and/or ptosis, or; a sense of restlessness or agitation. The diagnostic criteria for episodic cluster headache require at least 2 cluster periods lasting from 7 days to 1 year if untreated and separated by pain-free remission periods of ≥3 months. The diagnostic criteria for chronic cluster headache require cluster headaches occurring for 1 year or more without remission, or with remission of less than 3 months. The age at onset for cluster headaches is generally 20 to 40 years and men are affected 3 times more often than are women.

Interventions
The therapy being considered is nVNS or tVNS as an adjunct to standard care for prevention of headache.

Noninvasive devices that transcutaneously stimulate the vagus nerve on the side of the neck have been developed. The patient administers nVNS using a handheld device by placing the device on the side of the neck, over the cervical branch of the vagus nerve and positioning the metal stimulation surfaces in front of the sternocleidomastoid muscle, over the carotid artery. The frequency and timing of stimulation vary depending on the indication. NVNS can be used multiple times a day.

Comparators
The standard of care (SOC) treatment to stop or prevent attacks of cluster headache is medical therapy. Guideline-recommended treatments for acute cluster headache attacks include oxygen inhalation and triptans (e.g., sumatriptan and zolmitriptan). Oxygen is preferred first-line, if available because there are no documented adverse effects for most

adults. Triptans have been associated with primarily nonserious adverse events; some patients experience nonischemic chest pain and distal paresthesia. Use of oxygen may be limited by practical considerations and the FDA approved labeling for subcutaneous sumatriptan limits use to 2 doses per day. Steroid injections may be used to prevent or reduce the frequency of cluster headaches. Verapamil is also frequently used for prophylaxis.

Given the high placebo response rate in cluster headache, trials with sham nVNS are most relevant.

Outcomes
The general outcomes of interest are headache intensity and frequency, the effect on function and quality of life and adverse events.

The most common outcome measures for prevention of cluster headache are decrease in headache days per month compared with baseline and the proportion of responders to the treatment, defined as those patients who report more than a 50%, 75% or 100% decrease in headache days per month compared to pre-treatment.

Review of Evidence

Randomized Controlled Trials
Gaul et al (2016) reported on the results of a randomized open-label study of tVNS for the prevention of chronic cluster headache. Forty-eight patients with chronic cluster headache were randomized to tVNS or individualized SOC. Transcutaneous VNS was to be used twice daily with the option of additional treatment during headaches. At 4 weeks, the tVNS group had a greater reduction in the number of headaches than the control group, resulting in a mean therapeutic gain of 3.9 fewer headaches per week (p=.02). Regarding response rate, defined as a 50% or more reduction in headaches, the tVNS group had a 40% response rate, and the control group had an 8.3% response rate (p<.001). The study lacked a sham placebo control group, which might have resulted in placebo response in the tVNS group. Gaul et al (2017) reported post-hoc, additional analyses of the PREVention and Acute treatment of chronic cluster headache (PREVA) study with varying definitions of response, eg, attack frequency reductions of ≥25%, ≥75%, or ≥100 from baseline. Response consistently favored nVNS regardless of definition.

Nonrandomized and Observational Studies
To assess longer-term outcomes, non-randomized or observational prospective studies that capture longer periods of follow-up than the RCTs (> 1 month) and/or larger populations (with minimum n of 20) were sought. No such studies were identified.

Section Summary
Transcutaneous (or noninvasive) VNS has been investigated for preventing cluster headaches in 1 RCT. The PREVA study of prevention of cluster headache in patients

with chronic cluster headache demonstrated a statistically significant increase in the proportion of patients with a 50% or greater reduction in the mean number of headache attacks and statistically significant reduction in the frequency of attacks for nVNS compared to SOC with a treatment period of 4 weeks. There was also an improvement in quality of life as measured by the EQ-5D. However, the study was not blinded.

There are few adverse events of nVNS and they are mild and transient.

Treatment of Cluster Headaches

Clinical Context and Therapy Purpose
The purpose of nVNS or tVNS is to non-invasively apply low-voltage electrical currents to stimulate the cervical branch of the vagus nerve. nVNS has been tested primarily in the setting of headache. NVNS has been proposed as an intervention to relieve pain in acute attacks of cluster headaches as an alternative to standard care and to reduce the frequency of attacks for cluster headaches as an adjunct to standard care.

Populations
The relevant population of interest is individuals with cluster headache, using nVNS for treatment. The International Headache Society's International Classification of Headache Disorders classifies types of primary and secondary headaches. A summary of cluster headache based on the International Classification of Headache Disorders criteria is below.

Cluster headaches are primary headaches classified as trigeminal autonomic cephalalgias that can be either episodic or chronic. The diagnostic criteria for cluster headaches, states that these are attacks of severe, unilateral orbital, supraorbital, and/or temporal pain that lasts 15 to 180 minutes and occurs from once every other day to 8 times a day and further requires for the patient to have had at least 5 such attacks with at least 1 of the following symptoms or signs, ipsilateral to the headache: conjunctival injection and/or lacrimation; nasal congestion and/or rhinorrhea; eyelid edema; forehead and facial sweating; miosis and/or ptosis, or; a sense of restlessness or agitation. The diagnostic criteria for episodic cluster headache requires at least 2 cluster periods lasting from 7 days to 1 year if untreated and separated by pain-free remission periods of ≥3 months. The diagnostic criteria for chronic cluster headache require cluster headaches occurring for 1 year or more without remission, or with remission of less than 3 months. The age at onset for cluster headaches is generally 20 to 40 years and men are affected 3 times more often than are women.

Interventions
The therapy being considered is nVNS or tVNS as an alternative to standard care for acute headache.

Noninvasive devices that transcutaneously stimulate the vagus nerve on the side of the neck have been developed. The patient administers nVNS using a handheld device by

placing the device on the side of the neck, over the cervical branch of the vagus nerve and positioning the metal stimulation surfaces in front of the sternocleidomastoid muscle, over the carotid artery. The frequency and timing of stimulation vary depending on the indication. nVNS can be used multiple times a day.

Comparators
The SOC treatment to stop attacks of cluster headache is medical therapy. Guideline-recommended treatments for acute cluster headache attacks include oxygen inhalation and triptans (e.g., sumatriptan and zolmitriptan). Oxygen is preferred first-line, if available because there are no documented adverse effects for most adults. Triptans have been associated with primarily nonserious adverse events; some patients experience nonischemic chest pain and distal paresthesia. Use of oxygen may be limited by practical considerations and the FDA approved labeling for subcutaneous sumatriptan limits use to 2 doses per day. Steroid injections may be used to reduce the frequency of cluster headaches.

Given the high placebo response rate in cluster headache, trials with sham nVNS are most relevant.

Outcomes
The general outcomes of interest are headache intensity and frequency, the effect on function and quality of life and adverse events.

The most common outcome measures for treatment of acute cluster headache are headache relief measured as a proportion of patients with reduction on a pain relief scale by a specified time (usually 15, 30, 60 or 120 minutes after administration), proportion of patients who are pain-free by a specified time, sustaining reduction or pain-free for 24 hours, time to reduction or pain-free, and use of rescue medication. IHS guidelines for RCTs of drugs for migraine recommends the proportion of patients with pain score of zero (pain-free) at 2 hours before rescue medication as the primary efficacy measure in RCTs with earlier time points also being considered.[59,] IHS guidelines also state that sustained pain freedom or relapse and recurrence within 48 hours is an important efficacy outcome and that standardized, validated tools to assess the changes in ability to function and quality of life should be secondary outcomes.

The effect of treatment on stopping acute headache should be measured over 15 minutes to 48 hours. Continued response may be measured over many months.

Review of Evidence

Randomized Controlled Trials
Two RCTs have evaluated nVNS for treatment of acute cluster headache compared to sham nVNS. Treatment periods ranged from 2 weeks to 1 month.

de Coo et al (2019) combined the data from ACT1 and ACT2 meta-analytically for the 2 primary outcomes reported in the 2 studies. The authors reported an interaction between treatment group and cluster headache subtype in the pooled analysis (p<.05 for both outcomes).

Goadsby et al (2018) reported on the results of randomized, double-blind, sham-controlled study (ACT2) for the treatment of acute cluster headache attacks. Ninety-two patients with cluster headaches were randomized to tVNS (described in this response as nVNS) or sham treatment. Patients were further identified as having episodic cluster headaches or chronic cluster headaches and randomized at approximately 1:1 to the tVNS and sham treatment groups. The primary efficacy endpoint was the ability to achieve pain-free status within 15 minutes of initiation of treatment without use of rescue treatment. There was no difference between tVNS-treated and sham-treated patients in the overall cluster headache study population. Subgroup analysis of the chronic cluster headache population showed no differences between tVNS-treated and sham-treated patients. For the episodic cluster headaches subgroup, tVNS demonstrated a 48% response rate compared with 6% response rate for sham-treated (p<.01). The interaction p-value for the subgroup analysis was statistically significant (p=.04).

Silberstein et al (2016) reported on the results of a randomized, double-blind, sham-controlled study (ACT1) for treatment of acute cluster headache attacks.[60,] One hundred fifty patients with cluster headaches were randomized to tVNS or sham treatment. Patients were further identified as having episodic cluster headaches or chronic cluster headaches and randomized at approximately 1:1 to the tVNS and sham treatment groups. The primary endpoint was response rate defined as the ability to achieve pain-free status within 15 minutes of initiation of treatment without rescue medication use through 60 minutes. Rescue medication was allowed after 15 minutes of nVNS or sham administration. There were no differences between tVNS-treated and sham-treated patients in the overall cluster headache study population. Subgroup analysis of the chronic cluster headache population showed no differences between tVNS-treated and sham-treated patients. For the episodic cluster headache subgroup, tVNS demonstrated a 34.2% response rate compared with 10.6% response rate for sham-treated (p=.008). An interaction p-value for the subgroup analysis was not reported.

Nonrandomized and Observational Studies
To assess longer-term outcomes, non-randomized or observational prospective studies that capture longer periods of follow-up than the RCTs (> 1 month) and/or larger populations (with minimum n of 20) were sought. No such studies were identified.

Section Summary
The ACT1 and ACT2 RCTs compared nVNS to sham for treatment of acute cluster headache in patients including both chronic and episodic cluster headache. The RCTs reported slightly different outcome measures so that consistencies in magnitude of treatment effects cannot be assessed. In ACT1, there was no statistically significant difference in the overall population in the proportion of patients with pain score of 0 or 1

at 15 minutes into the first attack (27% vs. 15%, p=.10) and no difference in the proportion of patients who were pain-free at 15 minutes in 50% or more of the attacks (12% vs. 7%, p=.33). However, in the episodic cluster headache subgroup (n=85) both outcomes were statistically significant favoring nVNS, although the interaction p-value was not reported. In ACT2 the proportion of attacks with a pain intensity score of 0 or 1 at 30 minutes was statistically significant overall (43% vs. 28%, p=.05). The proportion of attacks that were pain-free at 15 minutes was similar in the 2 treatment groups overall (14% vs. 12%) but a significant interaction was reported (p=.04). There was a statistically significantly higher proportion of attacks in the episodic subgroup that were pain-free at 15 minutes in the nVNS group compared to sham (48% vs. 6%, p<.01). Quality of life and functional outcomes have not been reported. Treatment periods ranged from only 2 weeks to 1 month with extended open-label follow-up of up to 3 months. Studies designed to test the effect of nVNS in the episodic subgroup with longer treatment and follow-up and including quality of life and functional outcomes are needed.

There are few adverse events of nVNS and they are mild and transient.

Treatment of Acute Migraines

Clinical Context and Therapy Purpose
The purpose of nVNS or tVNS is too non-invasively apply low-voltage electrical currents to stimulate the cervical branch of the vagus nerve. NVNS has been tested primarily in the setting of headache. NVNS has been proposed as an intervention to relieve pain in acute attacks of migraine headaches as an alternative to standard care and to reduce the frequency of attacks for migraine as an adjunct to standard care.

Populations
The relevant population of interest is individuals with migraine headache, using nVNS for treatment. The International Headache Society's International Classification of Headache Disorders classifies types of primary and secondary headaches. A summary of migraine headache based on the International Classification of Headache Disorders criteria is below.

Migraines are primary headaches that can occur with or without aura. Migraines without aura meet the following diagnostic criteria at least 5 attacks lasting 4 to 72 hours if untreated or unsuccessfully treated and with at least 2 of the following 4 features: unilateral location; pulsating quality; moderate or severe pain; aggravation by or causing avoidance of routine physical activity and having either nausea and/or vomiting and/or photophobia and phonophobia during the headache. The diagnostic criteria for migraine with aura requires 2 attacks with fully reversible visual, sensory, speech and/or language, motor, brainstem and/or retinal aura symptoms and at least 3 of the following: 1 or more aura symptoms spread gradually over ≥5 minutes; 2 or more aura symptoms in succession; each individual aura symptom lasts 5 to 60 minutes; 1 or more aura symptoms are unilateral; 1 or more aura symptoms are positive; the aura is accompanied,

or followed within 60 minutes, by headache. Migraines are most common in ages 30 to 39 and women are more frequently affected than men.

Interventions
The therapy being considered is nVNS or tVNS as an alternative to standard care for acute headache.
Noninvasive devices that transcutaneously stimulate the vagus nerve on the side of the neck have been developed. The patient administers nVNS using a handheld device by placing the device on the side of the neck, over the cervical branch of the vagus nerve and positioning the metal stimulation surfaces in front of the sternocleidomastoid muscle, over the carotid artery. The frequency and timing of stimulation vary depending on the indication. NVNS can be used multiple times a day.

Comparators
The SOC treatment to stop or prevent attacks of migraines is medical therapy.

SOC treatments for acute migraine attacks include analgesics and/or triptans. Antiemetics and ergots may be used as monotherapy or as an adjunct for treatment of acute migraine. Beta-blockers (e.g., metoprolol, propranolol, or timolol), antidepressants (e.g., amitriptyline or venlafaxine) and anticonvulsants (topiramate or sodium valproate) may be used to prevent or reduce the frequency of migraine attacks along with lifestyle measures. Choosing which preventive medical therapy to use depends on patient characteristics and comorbid conditions, medication adverse events, and patient preference. Calcitonin gene-related peptide antagonists have also been approved for migraine prevention.

Given the high placebo response rate in migraine headache, trials with sham nVNS are most relevant.

Outcomes
The general outcomes of interest are headache intensity and frequency, the effect on function and quality of life, and adverse events.The most common outcome measures for treatment of migraine headache are headache relief measured as a proportion of patients with reduction on a pain relief scale by a specified time (usually 15, 30, 60 or 120 minutes after administration), proportion of patients who are pain-free by a specified time, sustaining reduction or pain-free for 24 hours, time to reduction or pain-free, and use of rescue medication. IHS guidelines for RCTs of drugs for migraine recommends the proportion of patients with pain score of zero (pain-free) at 2 hours before rescue medication as the primary efficacy measure in RCTs with earlier time points also being considered. IHS guidelines also state that sustained pain freedom or relapse and recurrence within 48 hours is an important efficacy outcome and that standardized, validated tools to assess the changes in ability to function and quality of life should be secondary outcomes.

The effect of treatment on stopping acute headache should be measured over 15 minutes to 48 hours. Continued response may be measured over many months.

Review of Evidence

Randomized Controlled Trials
One randomized controlled trial (RCT) has evaluated nVNS for treatment of acute migraine headache compared to sham nVNS.

A prospective, multi-center, randomized, double-blind, sham-controlled study of gammaCore® Non-invasive Vagus Nerve Stimulator (nVNS) for the Acute Treatment of Migraine (PRESTO) trial was a multicenter, double-blind, randomized, sham-controlled trial of acute treatment of migraine with nVNS in 248 patients with episodic migraine with/without aura. The primary efficacy outcome was the proportion of participants who were pain-free without using rescue medication at 120 minutes. There was not a statistically significant difference in the primary outcome (30% vs. 20%; p =.07) although it favored the nVNS group. The nVNS group had a higher proportion of patients with a decrease in pain from moderate or severe to mild or no pain at 120 minutes (41% vs. 28%; p=.03) and a higher proportion of patients who were pain-free at 120 for 50% or more of their attacks (32% vs. 18%; p=.02). PRESTO results did not include quality of life or functional outcomes and the double-blind treatment and follow-up period was 4 weeks. In the additional 4 weeks of acute nVNS in the open-label period, rates of pain-free response after the first treated attack (28%,) and pain relief (43.4%) were similar to the rates in the double-blind period.

Nonrandomized and Observational Studies
To assess longer-term outcomes, non-randomized or observational prospective studies that capture longer periods of follow-up than the RCTs (> 2 months) and/or larger populations (with minimum n of 20) were sought.

Trimboli et al (2018) reported on the preventive and acute treatment of nVNS in 41 consecutive patients with refractory primary chronic headaches (n=23 with chronic migraine) in an open-label, prospective, noncomparative clinical audit. Response was defined as at least 30% reduction in headache days/episodes after 3 months of treatment. Two of 23 (9%) chronic migraine patients met the definition for responder.

Section Summary
One randomized controlled trials (RCT) has evaluated nVNS for acute treatment of migraine with nVNS in 248 patients with episodic migraine with/without aura. There was not a statistically significant difference in the primary outcome of the proportion of participants who were pain-free without using rescue medication at 120 minutes (30% vs. 20%; p =.07). However, the nVNS group had a higher proportion of patients with decrease in pain from moderate or severe to mild or no pain at 120 minutes (41% vs. 28%; p=.03) and a higher proportion of patients who were pain-free at 120 for 50% or more of their attacks (32% vs. 18%; p=.02). There are few adverse events of nVNS and

they are mild and transient. Quality of life and functional outcomes were not reported and the double-blind treatment period was 4 weeks with an additional 4 weeks of open-label treatment. Given the marginally significant primary outcome, lack of quality of life or functional outcomes and limited follow-up, further RCTs are needed.

Prevention of Migraine Headaches

Clinical Context and Therapy Purpose
The purpose of nVNS or tVNS is too non-invasively apply low-voltage electrical currents to stimulate the cervical branch of the vagus nerve. nVNS has been tested primarily in the setting of headache. nVNS has been proposed as an intervention to relieve pain in acute attacks of cluster or migraine headaches as an alternative to standard care and to reduce the frequency of attacks for both cluster headaches and migraine as an adjunct to standard care.

Populations
The relevant population of interest is individuals with migraine headache, using nVNS for prevention. The International Headache Society's International Classification of Headache Disorders classifies types of primary and secondary headaches. A summary of migraine headache based on the International Classification of Headache Disorders criteria is below.

Migraines are primary headaches that can occur with or without aura. Migraines without aura meet the following diagnostic criteria: at least 5 attacks lasting 4 to 72 hours if untreated or unsuccessfully treated and with at least 2 of the following 4 features: unilateral location; pulsating quality; moderate or severe pain; aggravation by or causing avoidance of routine physical activity, and having either nausea and/or vomiting and/or photophobia and phonophobia during the headache. The diagnostic criteria for migraine with aura requires 2 attacks with fully reversible visual, sensory, speech and/or language, motor, brainstem and/or retinal aura symptoms and at least 3 of the following: 1 or more aura symptoms spread gradually over ≥5 minutes; 2 or more aura symptoms in succession; each individual aura symptom lasts 5 to 60 minutes; 1 or more aura symptoms are unilateral; 1 or more aura symptoms are positive; the aura is accompanied, or followed within 60 minutes, by headache. Migraines are most common in ages 30 to 39 and women are more frequently affected than men.

Interventions
The therapy being considered is nVNS or tVNS as an alternative to standard care for acute headache or as an adjunct to standard care for prevention of headache.

Noninvasive devices that transcutaneously stimulate the vagus nerve on the side of the neck have been developed. The patient administers nVNS using a handheld device by placing the device on the side of the neck, over the cervical branch of the vagus nerve and positioning the metal stimulation surfaces in front of the sternocleidomastoid muscle,

over the carotid artery. The frequency and timing of stimulation vary depending on the indication. NVNS can be used multiple times a day.

Comparators
The SOC treatment to stop or prevent attacks of migraine is medical therapy.

SOC treatments for acute migraine attacks include analgesics and/or triptans. Antiemetics and ergots may be used as monotherapy or as an adjunct for treatment of acute migraine. Beta-blockers (e.g., metoprolol, propranolol, or timolol), antidepressants (e.g., amitriptyline or venlafaxine) and anticonvulsants (topiramate or sodium valproate) may be used to prevent or reduce the frequency of migraine attacks along with lifestyle measures. Choosing which preventive medical therapy to use depends on patient characteristics and comorbid conditions, medication adverse events, and patient preference. Calcitonin gene-related peptide antagonists have also been approved for migraine prevention.

Given the high placebo response rate in migraine headache, trials with sham nVNS are most relevant.

Outcomes
The general outcomes of interest are headache intensity and frequency, the effect on function and quality of life, and adverse events.

The most common outcome measures for prevention of cluster or migraine headache are decrease in headache days per month compared with baseline and the proportion of responders to the treatment, defined as those patients who report more than a 50%, 75% or 100% decrease in headache days per month compared to pre-treatment. IHS guidelines recommend 2 primary efficacy outcomes for migraine prevention: number of migraine attacks per evaluation interval and number of migraine days per evaluation interval.

The IHSC guidelines suggest that effect of treatment on preventing migraine headache should be measured over at least 3 months in phase II RCTs and up to 6 months in phase III RCTs.

Review of Evidence

Randomized Controlled Trials
The EVENT trial was a feasibility study of prevention with a sample size of 59 patients. It was not powered to detect differences in efficacy outcomes. For the outcome of response, defined as 50% or more reduction in the number of headache days, 10% of the patients in the nVNS group versus 0% in the sham group were responders; statistical testing was not performed.

The PREMIUM trial was a phase 3, multicenter, sham controlled RCT conducted in several European countries including patients who experienced 5 to 12 migraine days per

month. The study included a 4-week run-in period during which no treatment was administered; 477 participants entered the run-in. The criteria to remain eligible after run-in were not described in the publication. After run-in, 341 participants were randomized (nVNS, n=169 or sham, n=172) to a 12-week double-blind treatment period followed by a 24-week open-label period of nVNS. Patients administered two 120-second stimulations bilaterally to the neck with gammaCore, 3 times daily. NVNS was not statistically significantly superior to sham. with respect to the outcomes of reduction of at least 50% in migraine days from baseline to the last 4 weeks, reduction in number of migraine days from baseline to the last 4 weeks or acute medication days in the intention-to-treat population.

Nonrandomized and Observational Studies
To assess longer-term outcomes, non-randomized or observational prospective studies that capture longer periods of follow-up than the RCTs (> 2 months) and/or larger populations (with minimum n of 20) were sought.

Grazzi et al (2016) reported on the use of preventive nVNS in an open-label, prospective, noncomparative study of 56 women with menstrual migraine. The treatment period was 12 weeks. At the end of treatment, the mean number of headache days per month was reduced from baseline (7.2 to 4.7; $p < .01$). Twenty patients (39%; 95% CI, 26% to 54%) had a ≥ 50 % reduction in headache days.

Kinfe et al (2015) enrolled 20 patients with treatment-refractory migraine in this 3-month, open-label, prospective, noncomparative observational study of preventive nVNS. The number of headache days per month decreased from 14.7 to 8.9 ($p < .01$) between baseline and end of treatment (3 months). The migraine disability assessment score improved from 26 to 15 ($p < .01$).

Section Summary
Two randomized controlled trials (RCTs) have evaluated nVNS for prevention of migraine. The EVENT trial was a feasibility study of prevention of migraine that was not powered to detect differences in efficacy outcomes. It does not demonstrate the efficacy of nVNS for prevention of migraine. The PREMIUM trial was a phase 3, multicenter, sham-controlled RCT including 341 randomized participants with a 12-week double-blind treatment period. The results of PREMIUM demonstrated that nVNS was not statistically significantly superior to sham with respect to the outcomes of reduction of at least 50% in migraine days from baseline to the last 4 weeks, reduction in number of migraine days from baseline to the last 4 weeks, or acute medication days.

Other Neurologic, Psychiatric and Metabolic Disorders

Clinical Context and Therapy Purpose
The purpose of nVNS or tVNS is to non-invasively apply low-voltage electrical currents to stimulate the cervical branch of the vagus nerve. nVNS has been tested primarily in the

setting of headache. Proposed uses have been tested in other neurologic, psychiatric, or metabolic disorders as well.

Populations
The relevant population of interest is individuals with other neurologic, psychiatric, or metabolic disorders.

Interventions
The therapy being considered is nVNS or tVNS as an alternative to standard care for acute headache or as an adjunct to standard care for prevention of headache.

Noninvasive devices that transcutaneously stimulate the vagus nerve on the side of the neck have been developed. The patient administers nVNS using a handheld device by placing the device on the side of the neck, over the cervical branch of the vagus nerve and positioning the metal stimulation surfaces in front of the sternocleidomastoid muscle, over the carotid artery. The frequency and timing of stimulation vary depending on the indication. NVNS can be used multiple times a day.

Comparators
The SOC treatment for other neurologic, psychiatric, or metabolic disorders is medication and behavioral therapy.

Outcomes
The general outcomes of interest are symptoms, change in disease status, and the effect on function and quality of life and adverse events.

Review of Evidence

Epilepsy
Wu et al (2020) reported results of a systematic review and meta-analysis of 3 RCT's (N=280, range n=60 to 144) of transcutaneous VNS for the treatment of drug-resistant epilepsy. All treatment groups underwent a cymba conchae stimulus at a frequency of 20 to 30-Hz. The control groups received various kinds of sham stimulation at a frequency of 1 HZ, the same frequency stimulation as treatment but at the non-auricular vagus nerve area or no stimulation. Meta-analysis of all 3 included RCTs found that seizure frequency was significantly reduced with transcutaneous VNS (Mean Difference [MD]=-3.29; 95% CI, -6.31 to -0.27). However, meta-analysis of the 2 RCTs that reported responder rates (undefined) did not find a significant difference between the transcutaneous VNS and control groups (N=238; OR =1.47; 95% CI, 0.54 to 4.02]. All 3 RCTs assessed quality of life using the Quality of Life in Epilepsy Inventory (QOLIE)-31 scale but found no significant differences between treatment and control groups. Important limitations of the RCTs include imprecision, risk of confounding due to potentially imbalanced use of important nonprotocol interventions (i.e., concomitant antiepileptic drugs), and unacceptable flaws in outcome assessment (i.e., unspecified definition of response, between-group differences in measurement timing, lack of electroencephalography data).

Fibromyalgia
Kutlu et al (2020) reported results of an RCT that compared a home-based exercise treatment program with or without auricular VNS in 60 female patients in Turkey with fibromyalgia syndrome (auricular VNS n=30 and no auricular VNS n=30). The VNS was delivered at Beykoz Public Hospital's Department of Physical Therapy and Rehabilitation in 30-minute sessions on weekdays for 4 weeks. The home-based exercise program consisted of strengthening, stretching, isometric, and posture exercises that targeted the body and upper and lower extremities. When added to exercise, auricular VNS did not significantly improve mean scores on the Fibromyalgia Impact Questionnaire (37.27 vs. 41.93; p=.378) or on any 36-Item Short Form Health Survey subscales (e.g., Physical Function: 80.00 vs. 85.00; p=.167). An important limitation of this RCT is the lack of a sham control group.

Impaired Glucose Tolerance
Huang et al (2014) reported on results of a pilot RCT of a tVNS device that provides stimulation to the auricle for the treatment of impaired glucose tolerance. The trial included 70 patients with impaired glucose tolerance who were randomized to active or sham tVNS, along with 30 controls who received no tVNS treatment. After 12 weeks of treatment, patients who received active tVNS were reported to have significantly lower 2-hour glucose tolerance test results than those who received sham tVNS (7.5 mmol/L vs. 8 mmol/L; p=.004).

Psychiatric Disorders
Hasan et al (2015) reported on a randomized trial of tVNS for the treatment of schizophrenia. Twenty patients were assigned to active tVNS or sham treatment for 12 weeks. There was no statistically significant difference in the improvement of schizophrenia status during the observation period.

Shiozawa et al (2014) conducted a systematic review of studies evaluating the evidence related to transcutaneous stimulation of the trigeminal or vagus nerve for psychiatric disorders. Reviewers also included a fifth study in a data table, although not in their text or a reference list (Hein et al [2013]; previously described). Overall, the studies assessed were limited by small size and poor generalizability.

Hein et al (2013) reported on results of 2 pilot RCTs of a tVNS device for the treatment of depression, 1 of which included 22 subjects, and another assessed 15 subjects. In the first study, 11 subjects were randomized to active or sham tVNS. At 2-week follow-up, Beck Depression Inventory (BDI) self-rating scores in the active stimulation group decreased from 27.0 to 14.0 points (p<.001), while the sham-stimulated patients did not show significant reductions in BDI scores (31.0 to 25.8 points). In the second study, 7 patients were randomized to active tVNS, and 8 patients were randomized to sham tVNS. In this study, BDI self-rating scores in the active stimulation group decreased from 29.4 to 17.4 points (p<.05) after 2 weeks, while the sham-stimulated patients did not show a significant change in BDI scores (28.6 to 25.4 points). The authors did not report direct comparisons in BDI change scores between the sham- and active-stimulation groups. One

RCT of tVNS for treatment of major depressive disorder has been registered in clinicaltrials.gov with a completion date of July 2016 (NCT02562703) but appears to be unpublished.

Traumatic Brain Injury
Vagus nerve stimulation (VNS) is being investigated to augment recovery from traumatic brain injury. It is proposed that early stimulation of the vagus nerve accelerates the rate and extent of behavioral and cognitive recovery after fluid percussion brain injury in rats. Shi et. al. (2013) received FDA approval to conduct a pilot prospective randomized trial to demonstrate objective improvement in clinical outcome by placement of VNS in individuals who are recovering from severe traumatic brain injury. If this study demonstrates that VNS can be safely and positively impact outcome, then a larger randomized prospective crossover trial will be proposed.

There is currently an ongoing clinical trial NCT02974959, single center prospective randomized (1:1), double blind, sham controlled parallel arm pilot study to provide initial evidence of the use of the noninvasive vagus nerve stimulator (VNS) for treatment in patients recovering from concussion and moderate traumatic brain injury to improve clinical recovery. The study is comparing the safety and effectiveness of an active gammaCore treatment against sham treatment. This is a Phase I study, looking to recruit 30 participants with an estimated completion date of June 2019. Per clinicaltrials.gov this study shows recruitment status is complete and no results posted at this time (accessed September 2022).

Treatment of Upper-Limb Impairment due to Stroke
Wu et al (2020) reported results of a randomized, pilot sham controlled RCT in 21 patients (nVNS=10 and sham nVNS, n=11) with upper limb motor function impairment following subacute ischemic stroke. The mean Fugl-Meyer assessment–upper extremity scores increased by 6.90 with nVNS versus 3.18 points with sham after 15 days of intervention (Difference= -3.72 points; 95% CI, −5.12 to -2.32; p≤.001). The improvement in the mean Fugl-Meyer assessment–upper extremity scores remained significantly higher at both the 4-week (+7.70 vs. +3.36; p≤.001) and the 12-week (+7.40 vs. +4.18; p=.038) follow-ups. There was only 1 adverse event noted, which was that 1 patient in the nVNS group developed skin redness at an electrode point of contact.

Section Summary
Transcutaneous VNS has been investigated in small, randomized trials for several conditions. Some evidence for the efficacy of tVNS for epilepsy comes from a systematic review of 3 small RCTs, which reported lower seizure rates for active tVNS-treated patients than for sham controls. However, the lack of significant improvement in response rates and quality of life, coupled with important methodological limitations, preclude drawing conclusions about net health outcome. In the study of depression, a small RCT that compared treatment using tVNS with sham stimulation demonstrated some improvements in depression scores with tVNS; however, the lack of comparisons between groups limits conclusions that might be drawn. One RCT of tVNS for treatment

of major depressive disorder is registered (NCT02562703) but appears to be unpublished. A sham-controlled pilot randomized trial for impaired glucose tolerance showed some effect on glucose. A sham-controlled pilot randomized trial for upper limb motor function impairment following subacute ischemic stroke showed some improvement in upper extremity function. A small RCT that compared a home-based exercise treatment program with or without auricular VNS for fibromyalgia syndrome did not find any significant benefits on fibromyalgia or quality of life measures. There is currently an ongoing clinical trial NCT02974959, single center prospective randomized (1:1), double blind, sham controlled parallel arm pilot study to provide initial evidence of the use of the noninvasive vagus nerve stimulator (VNS) for treatment in patients recovering from concussion and moderate traumatic brain injury to improve clinical recovery.

Summary of Evidence

Vagus Nerve Stimulation
For individual who have seizures refractory to medical treatment that have received vagus nerve stimulation (VNS), the evidence includes randomized controlled trials (RCTs) and multiple observational studies. The RCTs have reported significant reductions in seizure frequency for patients with partial-onset seizures. The uncontrolled studies have consistently reported large reductions in a broader range of seizure types in both adults and children. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have treatment resistant depression who receive vagus nerve stimulation (VNS), the evidence includes randomized controlled trial (RCT), nonrandomized comparative studies, and case series. The sham controlled RCT only reported short-term results and found no significant improvement in the primary outcome. The low-dose VNS controlled trial reported no statistically significant differences between the dose groups for change in depression symptom score from baseline. Other available studies are limited by small sample sizes, potential selection bias, and lack of a control groups in the case series. The evidence is insufficient to determine the effects of the technology on net health outcomes.

For individuals who have chronic heart failure who receive vagus nerve stimulation (VNS), the evidence includes a systematic review including 4 randomized controlled trials (RCTs) and case series. Meta-analyses of the RCTs evaluating chronic heart failure found significant improvements in New York Heart Association functional class, quality of life, 6-minute walk-test, and N-terminal-pro brain natriuretic peptide levels in patients treated with VNS compared to control. An analysis of the ANTHEM-HF uncontrolled trial evaluated longer-term outcomes of VNS use in chronic heart failure. They found that left ventricular (LV) ejection fraction improved by 18.7%, 19.3%, and 34.4% at 12, 24, and 36 months, respectively, with high-intensity VNS. Individuals with low-intensity VNS only had significant improvement in LV ejection fraction at 24 months (12.3%). Although this data is promising, a lack of a no-VNS comparator group precludes drawing

conclusions based on findings from the uncontrolled studies. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have upper-limb impairment due to stroke who receive vagus nerve stimulation (VNS), the evidence includes 3 pilot RCTs. Two RCTs compared VNS plus rehabilitation to rehabilitation alone; 1 failed to show significant improvements for the VNS group on response and function outcomes, but the other, which had a larger patient population, found a significant difference in response and function outcomes. The other RCT compared VNS to sham and found that although VNS significantly improved response rate, there were 3 serious adverse events related to surgery. Longer-term follow-up studies are needed to evaluate long-term efficacy and safety. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have other neurologic conditions (e.g., essential tremor, headache, fibromyalgia, tinnitus, autism) who receive VNS, the evidence includes case series. Case series are insufficient to draw conclusions regarding efficacy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Transcutaneous Vagus Nerve Stimulation
For individuals with cluster headaches who receive transcutaneous VNS to prevent cluster headaches, the evidence includes 1 RCT. Relevant outcomes are symptoms, change in disease status, quality of life and functional outcomes. One RCT for prevention of cluster headache showed a reduction in headache frequency but did not include a sham treatment group. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with cluster headache who receive nVNS to treat acute cluster headache, the evidence includes RCTs. Relevant outcomes are symptoms, change in disease status, quality of life and functional outcomes. The ACT1 and ACT2 RCTs compared nVNS to sham for treatment of acute cluster headache in patients including both chronic and episodic cluster headache. In ACT1, there was no statistically significant difference in the overall population in the proportion of patients with pain score of 0 or 1 at 15 minutes into the first attack and no difference in the proportion of patients who were pain-free at 15 minutes in 50% or more of the attacks. In the episodic cluster headache subgroup (n=85) both outcomes were statistically significant favoring nVNS although the interaction p-value was not reported. In ACT2, the proportion of attacks with pain intensity score of 0 or 1 at 30 minutes was higher for nVNS in the overall population (43% vs. 28%, p=.05) while the proportion of attacks that were pain-free at 15 minutes was similar in the 2 treatment groups in the overall population (14% vs. 12%). However, a statistically significantly higher proportion of attacks in the episodic subgroup (n=27) were pain-free at 15 minutes in the nVNS group compared to sham (48% vs. 6%, p<.01). These studies suggest that people with episodic and chronic cluster headaches may respond differently to acute treatment with nVNS. Studies designed to focus on episodic cluster headache are needed. Quality of life and functional outcomes have not been

reported. Treatment periods ranged from only 2 weeks to 1 month with extended open-label follow-up of up to 3 months. There are few adverse events of nVNS and they are mild and transient. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with migraine headache who receive nVNS to treat acute migraine headache, the evidence includes 1 RCT. One RCT has evaluated nVNS for acute treatment of migraine with nVNS in 248 patients with episodic migraine with/without aura. There was not a statistically significant difference in the primary outcome of the proportion of participants who were pain-free without using rescue medication at 120 minutes (30% vs. 20%; p =.07). However, the nVNS group had a higher proportion of patients with decrease in pain from moderate or severe to mild or no pain at 120 minutes (41% vs. 28%; p=.03) and a higher proportion of patients who were pain-free at 120 for 50% or more of their attacks (32% vs. 18%; p=.02). There are few adverse events of nVNS and they are mild and transient. Quality of life and functional outcomes were not reported and the double-blind treatment period was 4 weeks with an additional 4 weeks of open-label treatment. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with chronic migraine headache who receive nVNS to prevent migraine headache, the evidence includes 2 RCTs. The EVENT RCT was a feasibility study of prevention of migraine that was not powered to detect differences in efficacy outcomes. It does not demonstrate the efficacy of nVNS for prevention of migraine. The PREMIUM RCT was a phase 3, multicenter, sham-controlled RCT including 341 randomized participants with a 12-week double-blind treatment period. The results of PREMIUM demonstrated that nVNS was not statistically significantly superior to sham with respect to the outcomes of reduction of at least 50% in migraine days from baseline to the last 4 weeks, reduction in number of migraine days from baseline to the last 4 weeks, or acute medication days. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have other neurologic, psychiatric, or metabolic disorders (e.g., epilepsy, depression, schizophrenia, noncluster headache, impaired glucose tolerance, fibromyalgia, stroke, traumatic brain injury) who receive transcutaneous VNS, the evidence includes RCTs and case series for some of the conditions. The RCTs are all small and have various methodologic problems. None showed definitive efficacy of transcutaneous VNS in improving patient outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Vagus Nerve Blocking Therapy for Treatment of Obesity

Clinical Context and Purpose

The purpose of vagal nerve blocking therapy for the treatment of obesity is to provide a treatment option that is an alternative to or an improvement on existing therapies.

Patients
The relevant population of interest is patients with morbid obesity who have been unsuccessful with lifestyle management for weight reduction.

Interventions
The intervention being considered is vagal nerve blocking therapy for the treatment of obesity. Vagus nerve blocking therapy involves the intermittent blocking of signals to the intra-abdominal vagus nerve, with the intent of disrupting hunger sensations and inducing feelings of satiety. Patients with obesity who receive vagal nerve blocking therapy would require follow-up for 6-12 months to ascertain weight loss success and early device complications. Follow-up of maintenance of weight loss or obesity-associated conditions are life-long.

Comparators
The following therapies and practices are currently being used to make decisions about the treatment of obesity; lifestyle interventions, specifically changes to diet and exercise, are the first-line treatment of obesity. These interventions can be enhanced by participation in a structured weight loss program and/or by psychological interventions such as cognitive-behavioral therapy. There are also prescription weight loss medications available, most notably orlistat (which blocks digestion and absorption of fat) and lorcaserin (which decreases appetite and promotes satiety). Weight loss medications have limited evidence of efficacy and there are adverse events (e.g., oily stool, nausea, dizziness) associated with their use. Weight loss (bariatric) surgery is a potential option for obese patients who have failed conservative treatments.

Outcomes
The general outcomes of interest are weight reduction and maintenance of weight reduction, disease status changes such as the development of medical complications of obesity, and treatment-related morbidity.

More than one-third (36.5%) of U.S. adults have obesity which is defined as a body max index (BMI) 30.0 or higher (based on the U.S. Centers for Disease Control and Prevention). Obesity is a major cause of premature death and is linked to serious illnesses including heart disease, type 2 diabetes, stroke, sleep apnea, osteoarthritis, and certain types of cancer. Lifestyle interventions, especially changes to diet and exercise are the first line treatment of obesity. These interventions can be enhanced by participating in a structured weight loss program and/or by psychological interventions. There are also prescription weight loss medications available which have limited evidence of efficacy and there are adverse effects associated with their use. Weight loss (bariatric) surgery is another potential option for patients who have failed conservative treatments.

Vagus nerve blocking therapy is being investigated as another potential treatment option for obese patients. The vagus nerve consists of 2 long cranial nerves that extend from the brain to the viscera. The vagus nerve winds through the abdomen and has branches that come into contact with the heart, lung, stomach, and other body parts. The vagus nerve

plays a major role in autonomic and sympathetic nervous system functioning, including regulation of heartbeat and breathing. It is also involved in regulation of the digestive system, although its exact role in controlling appetite and feelings of satiety is unknown. Vagus nerve blocking therapy involves intermittent blocking of signals to the intra-abdominal vagus nerve, with the intent of disrupting hunger sensations and inducing feelings of satiety.

In January 2015, the U.S. Food and Drug Administration (FDA) approved a medical device specifically designed to provide vagal nerve blocking therapy for regulation of weight in obese patients. This device, the Maestro Rechargeable system, includes neuroblocking pulse generator that is implanted subcutaneously on the thoracic sidewall and flexible leads approximately 47 cm in length that are placed on the abdominal anterior and posterior vagal nerve trunks. External components include mobile charger, a transmit coil, a programmable microprocessor, and customized software. The system delivers high-frequency pulses of electrical current to vagus nerve trunks; therapy parameters and the treatment schedule can be customized by a clinician. Like other surgical interventions, there is the potential for adverse effects. In addition, there may be other unintended consequences of disrupting signals to a particular portion of the vagus nerve.

The published literature on vagus nerve blocking for obesity consists of two randomized controlled trials (RCTs) (EMPOWER and ReCharge), both of which were industry sponsored, multicenter, double-blind and sham-controlled. Although both trials included a sham treatment group, protocols differed. In the 2012 EMPOWER trial, all participants had devices implanted and leads placed. However, external controllers were programmed differently such that if the controllers were worn for 10 hours a day, total charge delivered was 3.9 coulombs (C) to patients in the treatment and a negligible amount (0.0014 C), to the sham group. In the 2014 ReCharge trial, all participants had devices implanted, but no leads were placed in the sham group.

Sarr et. al. (2012) conducted a randomized, prospective, double-blind, multicenter trial of vagal blockade to induce weight loss in morbid obesity, the EMPOWER study. This controlled trial was conducted in the U.S. and Australia. Five hundred three subjects were enrolled at 15 centers. After informed consent, 294 subjects were implanted with the vagal blocking system and randomized to the treated (n = 192) or control (n = 102) group. Main outcome measures were percent excess weight loss (percent EWL) at 12 months and serious adverse events. Subjects controlled duration of therapy using an external power source; therapy involved a programmed algorithm of electrical energy delivered to the subdiaphragmatic vagal nerves to inhibit afferent/efferent vagal transmission. Devices in both groups performed regular, low-energy safety checks. Data are mean ± SEM (standard error of the mean). Study subjects consisted of 90 % females, body mass index of 41 ± 1 kg/m(2), and age of 46 ± 1 years. Device-related complications occurred in 3 % of subjects. There was no mortality. 12-month percent EWL was 17 ± 2 % for the treated and 16 ± 2 % for the control group. Weight loss was related linearly to hours of device use; treated and controls with ≥ 12 h/day use achieved

30 ± 4 and 22 ± 8 % EWL, respectively. The authors concluded, VBLOC therapy to treat morbid obesity was safe, but weight loss was not greater in treated compared to controls; clinically important weight loss, however, was related to hours of device use. Post-study analysis suggested that the system electrical safety checks (low charge delivered via the system for electrical impedance, safety, and diagnostic checks) may have contributed to weight loss in the control group.

Ikramuddin et. al. (2014) conducted a randomized, double-blind, sham-controlled clinical trial to evaluate the effectiveness and safety of intermittent, reversible vagal nerve blockade therapy for obesity treatment, the ReCharge study. This trial was conducted at 10 sites in the U.S. and Australia between May and December 2011. The 12-month blinded portion of the 5 year study was completed in January 2013. The trial involved 239 participants who had a body mass index of 40 to 45 or 35 to 40 and 1 or more obesity-related condition. One hundred sixty-two patients received an active vagal nerve block device and 77 received a sham device. All participants received weight management education. The co-primary efficacy objectives were to determine whether the vagal nerve block was superior in mean percentage excess weight loss to sham by a 10-point margin with at least 55% of patients in the vagal block group achieving a 20% loss and 45% achieving a 25% loss. The primary safety objective was to determine whether the rate of serious adverse events related to device, procedure, or therapy in the vagal block group was less than 15%. In the intent-to-treat analysis, the vagal nerve block group had a mean 24.4% excess weight loss (9.2% of their initial body weight loss) vs 15.9% excess weight loss (6.0% initial body weight loss) in the sham group. The mean difference in the percentage of the excess weight loss between groups was 8.5 percentage points (95% CI, 3.1-13.9), which did not meet the 10-point target (P = .71), although weight loss was statistically greater in the vagal nerve block group (P = .002 for treatment difference in a post hoc analysis). At 12 months, 52% of patients in the vagal nerve block group achieved 20% or more excess weight loss and 38% achieved 25% or more excess weight loss vs 32% in the sham group who achieved 20% or more loss and 23% who achieved 25% or more loss. The device, procedure, or therapy-related serious adverse event rate in the vagal nerve block group was 3.7% (95% CI, 1.4%-7.9%), significantly lower than the 15% goal. The adverse events more frequent in the vagal nerve block group were heartburn or dyspepsia and abdominal pain attributed to therapy; all were reported as mild or moderate in severity. The authors concluded, among patients with morbid obesity, the use of vagal nerve block therapy compared with sham control device did not meet wither of the prescribed co-primary efficacy objectives, although weight loss in the vagal block group was statistically greater than in the sham device group. The treatment was well tolerated, having met the primary safety objective.

The primary efficacy outcomes were not met in either RTC. The difference in mean percent excess weight loss (EWL) was the sole primary efficacy outcome in the EMPOWER study and a co-primary outcome in the ReCharge study. This outcome was evaluated in both trials using a superiority margin of 10% (i.e., the efficacy objective would be met only if there was > 10% difference between groups in EWL). U.S. Food and Drug Administration (FDA) documents (Summary of Safety and Effectiveness Data

[SEED]) have indicated that the unattained 10% margin was considered to indicate a clinically meaningful difference in weight loss between active and sham treatment groups.

The outcome used in these studies was percent EWL, and modest changes in this outcome may translate to a relatively small amount of weight loss relative to total weight for patients with morbid obesity. Mean initial body weight in the ReCharge trial was 113 kilograms (249 pounds) in the active treatment group and 116 kilograms (255 pounds) in the sham group. Mean excess body weight was 44 kilograms (97 pounds) in the treatment group and 45 kilograms (99 pounds) in the sham group. A difference of 10% EWL, used in the primary analyses, represents a difference of only about 5 kilograms (10 pounds) in absolute weight loss and a 4% difference in absolute body weight.

Additional information on the ReCharge trial design and findings has been reported in FDA documents (Summary of Safety and Effectiveness Data [SEED]). The trial was designed to evaluate primary end points at 12 months and to follow patients for 5 years post implant. Patients were blinded until 12 months and unblinding began once all patients had completed the 12- month follow-up. After the 12- month follow-up, sham patients had the option to cross over into the active treatment group. At 18 months, follow-up data (n=159) were reported for 117 (72%) patients initially assigned to the active treatment group and 42 (55%) assigned to the sham treatment group. The number of patients in the sham group who crossed over to active treatment and the timing of unblinding were not reported. At 18 months, the mean percent EWL (excess weight loss) was 25.3% in the active treatment group and 11.7% in sham group; the mean between group difference was 13.5% (95% CI, 5.7% to 21.3%). In this analysis, the treatment group maintained the weight loss they achieved at 12 months, and the control group gained weight. Nearly half of the patients initially randomized to the sham group were not included in the 18- month analysis, which limits ability to draw conclusions about these data. In addition, the 18- month analysis could have been biased by unblinding, which occurred after all patients completed the 12-month follow-up. In the 12- month sham intervention phase of the trial, patients in both groups experienced decreased hunger, increased cognitive restraint, and decreased food intake. It is likely that unblinding could have had an impact on these factors. FDA documents also reported longer term safety data. Analyses of data up to 48 months from the EMPOWER trial and 18- month data from the ReCharge trial did not identify any deaths or unanticipated serious adverse events. There were 13 surgical explants through 12 months (5 in active treatment group, 8 in sham group) and an additional 16 explanations between 12 and 18 months. Reasons for explant included patient decision, pain, and need for MRI.

In 2015, Shikora et. al. published the 18- month follow-up data from the ReCharge trial. They reported on a larger proportion of the patient population than that discussed in the FDA documents: in addition to the 159 (67%) of 239 randomized patients who completed the 18- month follow-up, the 2015 analysis included 30 patients who missed the 18-month analysis but had a visit at 16 or 17 months. The additional patients included 11 from the active treatment group and 19 from the sham group, comprising 188 patients

(79% of those originally randomized). At 18 months, the mean percent EWL noted was 23.5% (95% CI, 20.8% to 26.3%) in the active treatment group and 10.2% (95% CI, 6.0% to 14.4%) in the sham group. The mean between group difference in percent EWL was 13.4% (95% CI, 8.4% to 18.4%). The authors also evaluated the potential impact of blinding on outcomes and found no statistically significant effect; their findings were similar to the analysis restricted to patients who remained blinded at 18 months. The percentages of EWL at 18 months in this 2015 analysis of ReCharge trial data were also similar to those previously reported in FDA documents, although this sample size was larger, reducing potential bias from missing data. The authors concluded, follow-up through 18 months of the ReCharge study showed sustained weight loss with intermittent vagal nerve block but not with sham surgery and device intervention. vBloc therapy continued to be safe and well tolerated. Additional long-term data and continued follow-up of the ReCharge study are needed to further characterize the safety and effectiveness profile of vBloc therapy.

Apovian et. al. (2017) published two- year outcomes of vagal nerve blocking (vBloc) for the treatment of obesity in the ReCharge trial. Participants with body mass index (BMI) 40 to 45 kg/m^2, or 35 to 40 kg/m^2 with at least one comorbid condition were randomized to either vBloc therapy or sham intervention for 12 months. After 12 months, participants randomized to vBloc continued open label vBloc therapy and are the focus of this report. Weight loss, adverse events, comorbid risk factors, and quality of life (QOL) will be assessed for 5 years. The investigators noted that the sham arm was no longer a valid comparator at 24 months due to crossovers, dropouts, and patient unblended at 12 months. Participants who presented at 24 months (n = 103) had a mean excess weight loss (EWL) of 21 % (8 % total weight loss [TWL]); 58 % of participants had ≥5 % TWL and 34 % had ≥10 % TWL. Among the subset of participants with abnormal preoperative values, significant improvements were observed in mean LDL (-16 mg/dL) and HDL cholesterol (+4 mg/dL), triglycerides (-46 mg/dL), HbA1c (-0.3 %), and systolic (-11 mmHg) and diastolic blood pressures (-10 mmHg). QOL measures were significantly improved. Heartburn/dyspepsia and implant site pain were the most frequently reported adverse events. The primary related serious adverse event rate was 4.3 %. The analysis lacked a blinded comparison group, and, like the 18- month data, was post hoc.

Summary of Evidence

For individuals with obesity who receive vagus nerve blocking therapy, the evidence includes 2 sham-controlled randomized trials. The primary efficacy outcome (at least a 10% difference between groups at 12 months) was not met for either trial. In the first trial (EMPOWER), the observed differences in excess weight loss (EWL) between groups at 12 months was 1%. In the more recent trial (ReCharge), the observed difference in excess weight loss (EWL) between groups at 12 months was 8.5%; a post hoc analysis found this difference statistically significant, but the magnitude of change may not be viewed as clinically significant according to investigators original trial decisions. Post hoc analysis of longer- term data have been published and are subject to various biases, including missing data and unblinding at 12 months. Based on the trials the treatment was well tolerated, having met the primary safety objective. Additional studies are needed to

compare effectiveness of vagal nerve blocking therapy with other obesity treatments and to assess long-term durability of weight loss and safety. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Practice Guidelines and Position Statements

American Academy of Neurology (AAN)
In 2013 (reaffirmed 2019), the American Academy of Neurology (AAN) issued an evidence-based guideline update on vagus nerve stimulation for the treatment of epilepsy, that stated:

- Vagal nerve stimulation (VNS) may be considered as adjunctive treatment for children with partial or generalized epilepsy. VNS may be considered a possibly effective option after a child with medication resistant epilepsy has been declared a poor surgical candidate or has had unsuccessful surgery.
- VNS may be considered in patients with LGS [Lennox-Gastaut-syndrome]-associated seizures. The responder rate for patients with LGS does not appear to differ from that of general population of patients with medication resistant epilepsy.
- In adult patients receiving VNS for epilepsy, improvement in mood may be an additional benefit.

American Psychiatric Association (APA):
The American Psychiatric Association guidelines on treatment of major depressive disorder in adults, updated in November 2010, includes the following statement on the use of VNS: "electroconvulsive therapy (ECT) remains the treatment of best-established efficacy against which other stimulation treatments (e.g. vagus nerve stimulation (VNS), deep brain stimulation, transcranial magnetic stimulation, other electromagnetic stimulation therapies) should be compared. Vagus nerve stimulation (VNS) may be an additional option for individuals who have not responded to at least four adequate trials of antidepressant treatment, including ECT, with a level of evidence III (May be recommended on the basis of individual circumstances)."

American Society for Metabolic and Bariatric Surgery
In 2016, the American Society for Metabolic and Bariatric Surgery published a position statement that included the following conclusions and recommendations on vagus nerve blocking therapy for the treatment of obesity:

- Reversible vagal nerve blockade has been shown to result in statistically significant excess weight loss (EWL) at 1 year compared with a control group in one of 2 prospective randomized trials.
- Reversible vagal nerve blockade has been shown to have a reasonable safety profile with a low incidence of severe adverse events and a low revisional rate in the short term. More studies are needed to determine long-term reoperation and explanation rates.
- The prospective collection of VBLOC (vagus nerve blocking) outcomes as part of the national center of excellence databases is encouraged to establish the long-term efficacy of this new technology.

Regulatory Status
In 1997, the NeuroCybernetic Prosthesis (NCP) system (Cyberonics), a vagus nerve stimulation (VNS) device was approved the U.S. Food and Drug Administration (FDA) through the premarket approval (PMA) process for use in conjunction with drugs or surgery, as adjunctive treatment for adults and children 12 years of age and older with medically refractory partial onset seizures.

July 2005, Cyberonics received PMA supplement approval by FDA for the VNS therapy system for the adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments.

Cerbomed has developed a transcutaneous vagal nerve stimulator (tVNS) system that uses a combined stimulation unit and ear electrode to stimulate the auricular branch of the vagus nerve, which supplies the skin over the concha of the ear. Patients self- administer electrical stimulation for several hours a day; no surgical procedure is required. The device received European clearance (CE mark) in 2011, but has not been FDA approved for use in the United States.

January 2015 Maestro Rechargeable System (EnteroMedics, St. Paul, MN) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process for use in adults aged 18 years and older who have a body mass index (BMI) of 40 to 45 kg/m^2 or a BMI of 35 to 39.9 kg/m^2 with 1 or more obesity related conditions such as high blood pressure or high cholesterol and have failed at least 1 supervised weight management program within the past 5 years. Implantable components are incompatible with magnetic resonance imaging. Additional contraindications to use of the device include conditions such as cirrhosis of the liver, portal hypertension and clinically significant hiatal hernia, and the presence of a previously implanted medical device. FDA product code: PIM.

The commercial availability of the Maestro System is unclear. On the FDA's Weight-Loss and Weight-Management Devices webpage (content noted as current as of 09/05/2019), the Maestro Rechargeable System is described as "no longer marketed as of September 2018". Additionally, on the ReShape Lifesciences website (previously EnteroMedics), the Maestro Rechargeable System, is not listed among their current portfolio of medical devices to treat obesity and metabolic disease. However, updates to the Maestro Rechargeable System were noted in the FDA Premarket Approval database (P130019) subsequent to September 2018, including updates to the circuit assembly and application firmware of the mobile charger (01/25/2019) and approval of modifications to the follow-up schedule for the post-approval study protocol.

April 2017, the U.S. Food and Drug Administration (FDA) approved gammaCore Non-invasive Vagus Nerve Stimulator (ElectroCore LLC, Basking Ridge, New Jersey) intended to provide non-invasive vagus nerve stimulation (nVNS) on the side of the neck.

The gammaCore device is indicated for the acute treatment of pain associated with episodic cluster headache in adult patients.

PRIOR APPROVAL

Not applicable.

POLICY

Implantable Vagus Nerve Stimulation (VNS)

Implantable vagus nerve stimulation (VNS) may be considered **medically necessary** when **ALL** the following criteria are met:

- Patient has medically refractory seizures; **and**
- Surgery has failed **or** the individual is not a candidate for surgery.

Note: Medically refractory seizures are defined as seizures that occur despite therapeutic levels of antiepileptic drugs or seizures that cannot be treated with therapeutic levels of antiepileptic drugs because of intolerable adverse effects of these drugs.

Replacement and Revisions
Replacement or revisions of an implantable vagus nerve stimulator (VNS) and/or leads is considered medically necessary in an individual that meets the above criteria and the existing generator/lead/electrodes/programmer is no longer under warranty and/or cannot be repaired.

Vagus Nerve Stimulation (VNS) is considered **investigational** as treatment of all other conditions, including but not limited to the following because the evidence is insufficient evidence to determine the effects of the technology on net health outcomes:

- Autism
- Bipolar disorders
- Chronic heart failure
- Essential tremor
- Fibromyalgia
- Headaches
- Obesity
- Tinnitus
- Treatment resistant depression
- Upper limb impairment due to stroke

Transcutaneous Vagus Nerve Stimulation (tVNS)
Transcutaneous vagus nerve stimulation (tVNS)) (nonimplantable) devices are considered **investigational** for all indications, including but not limited to the following

because the evidence is insufficient evidence to determine the effects of the technology on net health outcomes:

- Depression
- Epilepsy
- Headaches: episodic cluster headaches; migraines
- Impaired glucose tolerance
- Schizophrenia
- Traumatic brain injury
- Upper limb impairment due to stroke

Vagus Nerve Blocking Therapy
Intra-abdominal vagus nerve blocking therapy is considered **investigational** for all indications, including but not limited to the treatment of obesity.

Based on the peer reviewed medical literature the evidence includes two sham-controlled randomized trials in which the primary efficacy outcome was not met for either trial. Additional studies are needed to compare effectiveness of vagal nerve blocking therapy with other obesity treatments and to assess long-term durability of weight loss and safety. The evidence is insufficient to determine the effects of this technology on net health outcomes.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 61885 Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to single electrode array.
- 61886 with connection to 2 or more electrode arrays.
- 64553 Percutaneous implantation of neurostimulator electrode array; cranial nerve
- 64569 Revision or replacement of cranial nerve (e.g. vagus nerve) neurostimulator electrode array, including connection to existing pulse generator.
- 64568 Open implantation of cranial nerve (e.g., vagus nerve) neurostimulator electrode array and pulse generator
- C1767 Generator neurostimulator (implantable) non-rechargeable
- C1778 Lead, neurostimulator (implantable)
- C1787 Patient programmer, neurostimulator
- C1816 Receiver and/or transmitter, neurostimulator (implantable)
- C1820 Generator, neurostimulator (implantable), non-high-frequency with rechargeable battery and charging system
- C1822 Generator, neurostimulator (implantable), high frequency with rechargeable battery and charging system
- C1897 Lead, neurostimulator test kit (implantable)
- L8679 Implantable neurostimulator, pulse generator any type

- L8680 Implantable neurostimulator electrode, each
- L8681 Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only
- L8682 Implantable neurostimulator radiofrequency receiver
- L8683 Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
- L8685 Implantable neurostimulator pulse generator, single array, rechargeable includes extension
- L8686 Implantable neurostimulator pulse generator, single array, nonrechargeable, includes extension
- L8687 Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
- L8688 Implantable neurostimulator pulse generator, dual array, nonrechargeable, includes extension
- L8689 External recharging system for battery (internal) for use with implantable neurostimulator, replacement only
- L8687 Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
- E1399 Durable medical equipment, miscellaneous (when specified as non-implantable vagus nerve stimulation (VNS) or transcutaneous vagus nerve stimulation [tVNS])
- K1020 Non-invasive vagus nerve stimulator
- 95970 Electronic analysis of implanted neurostimulator pulse generator system (e.g., contact group(s), interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain, cranial nerve, spinal cord, peripheral nerve or sacral nerve neurostimulator pulse generator/transmitter, without programming
- 95976 Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group(s), interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with simple cranial nerve neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional
- 95977 Electronic analyses of implanted neurostimulator pulse generator/transmitter (e.g., contact group(s), interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional

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POLICY HISTORY		
Date	**Reason**	**Action**
September 2022	Annual Review	Policy Renewed
September 2021	Annual Review	Policy Renewed
September 2020	Annual Review	Policy Renewed
September 2019	Annual Review	Policy Renewed
September 2018	Annual Review	Policy Revised
September 2017	Annual Review	Policy Revised

September 2016	Annual Review	Policy Revised
October 2015	Annual Review	Policy Revised
February 2015	Interim Review	Policy Revised
November 2014	Annual Review	Policy Revised
January 2014	Annual Review	Revision & New Policy Created
January 2013	Annual Review	Policy Renewed
January 2012	Annual Review	Policy Renewed
February 2011	Annual Review	Policy Revised
October 2010	Annual Review	Policy Renewed

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

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
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