Policy Number	**SUR712.021**
Policy Effective Date	**01/01/2025**

Vagus Nerve Stimulation (VNS)

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Related Policies (if applicable)
SUR716.003: Bariatric Surgery

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For Illinois only: Illinois Public Act 103-0458 [Insurance Code 215 ILCS 5/356z.61] (HB3809 Impaired Children) states all group or individual fully insured PPO, HMO, POS plans amended, delivered, issued, or renewed on or after January 1, 2025 shall provide coverage for therapy, diagnostic testing, and equipment necessary to increase quality of life for children who have been clinically or genetically diagnosed with any disease, syndrome, or disorder that includes low tone neuromuscular impairment, neurological impairment, or cognitive impairment.

Coverage

Vagus nerve stimulation (VNS) **may be considered medically necessary** as a treatment of medically refractory seizures.

Vagus nerve stimulation **is considered experimental, investigational and/or unproven** as a treatment of other conditions, including but not limited to depression, heart failure, upper-limb impairment due to stroke, essential tremor, headaches, fibromyalgia, tinnitus and traumatic brain injury.

Transcutaneous (nonimplantable) vagus nerve stimulation devices **are considered experimental, investigational and/or unproven** for all indications.

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EXCEPTION: The gammaCore Sapphire CV was issued an **emergency use authorization** (EUA) by the U.S. Food and Drug Administration (FDA) for acute use at home or in a healthcare setting to treat adult patients with known or suspected COVID-19 who were experiencing exacerbation of asthma-related dyspnea and reduced airflow, and for whom approved drug therapies were not tolerated or provided insufficient symptom relief as assessed by their healthcare provider.

Per the FDA EUA, the gammaCore Sapphire CV is not intended for use in patients with:

- An active implantable medical device, such as a pacemaker, hearing aid implant or any implanted electronic device; OR,
- A metallic device, such as a stent, bone plate, or bone screw, implanted at or near the neck; OR,
- An open wound, rash, infection, swelling, cut, sore, drug patch, or surgical scar(s) on their neck at the treatment location.

The COVID-19 public health emergency (PHE) expired on May 11, 2023. The FDA released a phased transition plan for medical devices with the expectation that manufacturers be in full compliance with FDA requirements 180 days after the PHE expiration, if they intended to continue marketing their device.

Policy Guidelines

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 events of these drugs.

Vagus nerve stimulation has been evaluated for the treatment of obesity. This indication is addressed in medical policy SUR716.003 (Bariatric Surgery).

Description

Stimulation of the vagus nerve can be performed using a pulsed electrical stimulator implanted within the carotid artery sheath. This technique has been proposed as a treatment for refractory seizures, depression, and other disorders. There are also devices available that are implanted at different areas of the vagus nerve. This medical policy also addresses devices that stimulate the vagus nerve transcutaneously.

Background

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.

While the mechanisms for the therapeutic effects of VNS are not fully understood, the basic premise of VNS in the treatment of various conditions is that vagal visceral afferents have a diffuse central nervous system projection, and activation of these pathways has a widespread effect on 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 provide parasympathetic innervation to the gastrointestinal tract.

Other types of implantable vagus nerve stimulators that are placed in contact with the trunks of the vagus nerve at the gastroesophageal junction are not addressed in this medical policy.

Regulatory Status

Table 1 includes updates on the U.S. Food and Drug Administration (FDA) approval and clearance for VNS devices pertinent to this medical policy.

Table 1. FDA Approved or Cleared Vagus Nerve Stimulators

Device Name	Manufacturer	Approved/ Cleared	PMA/510K	Product Code(s)	Indications
NeuroCybernetic Prosthesis (NCP®)/VNS Therapy®	LivaNova (Cyberonics)	1997	P970003	LYJ, MUZ	Indicated for adjunctive treatment of adults and adolescents >12 years of age with medically refractory partial-onset seizures.
		2005	P970003/S50		Expanded indication for adjunctive long-term treatment of chronic or recurrent depression for patients ≥18 years of age experiencing a major depressive episode and have not had an adequate response to ≥4 adequate

					antidepressant treatments.
		2017	P970003/ S207		Expanded indicated use as adjunctive therapy for seizures in patients ≥4 years of age with partial-onset seizures that are refractory to antiepileptic medications.
gammaCore®	ElectroCore	2017/2018	DEN150048/ K171306/ K173442	PKR, QAK	Indicated for acute treatment of pain associated with episodic cluster and migraine headache in adults using noninvasive VNS on the side of the neck.
gammaCore-2®, gammaCore-Sapphire®	ElectroCore	2017/2018/ 2021	K172270/ K180538/ K182369/ K191830/ K203456/ K211856	PKR	Indicated for: • Adjunctive use for the preventive treatment of cluster headache in adult patients. • The acute treatment of pain associated with episodic cluster headache in adult patients. • The acute treatment of pain associated with migraine headache in adult patients. • The preventive treatment of migraine headache in adult patients.
MicroTransponder ® Vivistim® Paired	MicroTransponder Inc.	2021	210007	QPY	The device is intended to be used

VNS™ System (Vivistim® System) (1)					to stimulate the vagus nerve during rehabilitation therapy in order to reduce upper extremity motor deficits and improve motor function in chronic ischemic stroke patients with moderate to severe arm impairment.

FDA: U.S. Food and Drug Administration; PMA: premarket approval; VNS: vagus nerve stimulation.

In July 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the gammaCore Sapphire CV for use only during the COVID-19 pandemic and public health emergency. The EUA states in part "Based on the totality of scientific evidence available to FDA, it is reasonable to believe that the gammaCore Sapphire CV may be effective for acute emergency use at home or in a healthcare setting to treat adult patients with known or suspected COVID-19 who are experiencing exacerbation of asthma-related dyspnea and reduced airflow, and for whom approved drug therapies are not tolerated or provide insufficient symptom relief as assessed by their HCP [healthcare provider], by using non-invasive Vagus Nerve Stimulation (nVNS) on either side of the patients neck, and that the known and potential benefits of this product for such use outweigh the known and potential risks of such product; and, there are no adequate, approved, and available device alternatives to the emergency use of the gammaCore Sapphire CV for such use." (2)

Rationale

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is

preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice. The following is a summary of the key literature to date.

VAGUS NERVE STIMULATION

Treatment-Resistant Seizures

Clinical Context and Therapy 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.

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

Populations

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

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, is intolerant of medical standard therapy, or had failed resective surgery.

For treatment of refractory epilepsy, the following practices are currently being used: resective surgery, additional trials of conventional antiepileptic drugs and/or a 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, medication use and treatment-related morbidity.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Systematic Reviews

Reports on the use of VNS to treat medication-resistant seizure disorders date to the 1990s and were coincident with preapproval and early postapproval study of the device. Characteristics of systematic reviews are shown in Table 2. Results are shown in Tables 3 and 4.

Panebianco et al. (2015) updated a Cochrane systematic review and meta-analysis of VNS to treat partial seizures. (3) Reviewers specifically evaluated randomized, double-blind, parallel or crossover, controlled trials of VNS as add-on treatment comparing high- and low-stimulation paradigms plus VNS stimulation with no stimulation or different intervention. Five trials (N=439) compared high-frequency stimulation with low-frequency stimulation in participants ages 12 to 60 years, and another trial compared high-frequency stimulation with low-frequency stimulation in children. Results are shown in Table 3. Risk of bias was rated as low for most domains across studies. However, none of the protocols for the included studies were available and therefore were rated as having an unclear risk of bias for selective reporting. In addition, all studies were sponsored by the manufacturers of the device. An updated Cochrane systematic review published in 2022 by the same author group did not identify any new RCTs. (4)

Table 2. Characteristics of Systematic Reviews of Implantable VNS for Epilepsy

Study	Dates	Studies	Participants	N (Range)	Design	Duration
Panebianco et al. (2015, 2022) (3, 4)	Up to March 2022	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) (5)	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.

Table 3. Results of Systematic Reviews of RCTs of Implantable VNS for Epilepsy

Study	50% or greater	VNS Treatment	Voice Alteration	Cough	Dyspnea

	reduction in seizure frequency	withdrawal	or Cough		
Panebianco et al. (2015) (3)					
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)
I^2 (p[a])	18% (p=0.30)	0% (p=0.74)	32% (p=0.23)	0% (p=0.54)	0% (p=0.77)

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

Englot et al. (2011) conducted a systematic review of the literature through November 2010 assessing the efficacy of VNS and its predictors of response. (5) Fifteen RCTs and prospective observational studies were included. Analyses combined different study types. Given that the meta-analysis of RCTs is described in the Cochrane review, the observational studies only from the Englot et al. review are shown in Table 4.

Table 4. Summary of Prospective Studies Included in Systematic Review

Study (year)	N	Duration of FU	Number of sites	Seizure Type	Seizure Frequency Reduction >50%, %
Ben-Menachem et al. (1999) (6)	64	3-64 mo	Single	Mixed	45
Parker et al. (1999) (7)	15[a]	1 y	Single	Mixed	27
Labar et al. (1999) (8)	24	3 mo	Single	Generalized	46
DeGiorgio et al. (2000) (9)	195	12 mo	Multisite	Mixed	35
Chavel et al. (2003) (10)	29	1-2 y	Single	Partial	54[b]
Vonck et al. (1999) (11); (2004) (12)	118	>6 mo	Multisite	Mixed	50
Majoie et al. (2001) (13); (2005) (14)	19[a]	2 y	Single	Mixed	21
Huf et al. (2005) (15)	40[c]	2 y	Single	NR	28
Kang et al. (2006) (16)	16[d]	>1 y	Multisite	Mixed	50
Ardesch et al. (2007) (17)	19	>2 y	Single	Partial	33[e]

Adapted from Englot et al. (2011). (5)
FU: follow-up; mo: months; NR: not reported; y: year(s).
[a] Children with encephalopathy.
[b] Rate at 1-year follow-up.
[c] Adults with low IQ.
[d] Children.

[e] Rate at 2 years.

Randomized Controlled Trials

As noted in the previous section, 5 RCTs (N=439) have evaluated 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 of the trials are shown below in Table 5. Results are shown in Table 6.

Table 5. Characteristics of Double-Blind RCTs of VNS for Epilepsy

Study	Dates	Participants	Interventions	
			Active	***Comparator***
Michael et al. (1993) (18)	NR	Patients with refractory partial seizures (race or ethnicity not reported)	n=10 High stimulation	n=12 Low stimulation
Ben-Menchem et al./VNS Study Group (1994, 1999) (19, 6)	~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
Handforth et al. (1998) (20)	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, 5% race/ethnicity not reported)	n=95 High stimulation	n=103 Low stimulation
DeGiorgio et al. (2005) (9)	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
Klinkenberg et al. (2012) (21)	NR	Children with medically refractory epilepsy not eligible for epilepsy surgery (race or ethnicity not reported)	n=21 High output	n=20 Low output

N: number; 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.

Table 6. Results of Double-Blind RCTs of VNS for Epilepsy

Study	50% or greater reduction in seizure frequency (%)	Change in Seizure Frequency	Quality of life	Functional Outcomes
Michael et al. (1993) (18)				
N	22	NR	NR	NR
High stimulation	30%			
Low stimulation	0%			
Treatment effect (95% CI)	RR=8.27 (0.48 to 143.35)			
Ben-Menchem/VNS Study Group (1994, 1999) (19, 6)				
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=0.03		
Handforth et al. (1998) (20)			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=0.04	Difference=4.0 mm (0.6 to 7.4); p=0.02	
DeGiorgio et al. (2005) (9)		Median % reduction at 3 months		
N	42	NR	NR	NR
Rapid cycle	32%	-26%		
Slow cycle	26%	-29%		

Treatment effect (95% CI)	NR	NR		
Klinkenberg et al. (2012) (21)				
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=0.61		

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. (22)

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. (23) 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 Table 7. These rates did not differ statistically from participants with predominantly partial seizures.

Table 7. Summary of VNS Registry Outcomes

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

VNS: vagus nerve stimulation; mo: month(s).

[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. (24) 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.

Table 8 summarizes the evaluable literature on VNS in pediatric populations of all seizure types.

Table 8. Summary of VNS Pediatric Studies

Author (Year)	Study Type	Sample	Seizure Disorder Type	Duration of Follow-up	SFR ≥50% or Median Reduction, n (%)[a]	Notes
Hornig et al. (1997) (25)	Case series	19	Mixed	2-30 mo	10 (53)	Prior failed resective surgery: n=3

Murphy et al. (1999) (26)	Prospective OBS	60	Mixed	18 mo	46 (42)[a]	Age: 26% <12 y
Patwardhan et al. (2000) (27)	Case series	38	Mixed	12 mo (median)	26 (68)	Age: 11 mo to 16 y
Frost et al. (2001) (28)	Retrospective case review	50	LGS	6 mo	50 (57.9)[a]	Age: 13 y (median)
You et al. (2007) (29)	Prospective OBS	28	Mixed	31.4 mo (mean)	15 (53.6)	Age range: 2-17 y
Klinkenberg et al. (2012) (21)	RCT[b]	41	Mixed	19 wk	High-stim: 3/21(14.2) Low-stim: 4/20 (20)	Age range: 3-17 y
Cukiert et al. (2013) (30)	Case series	24	LGS	24 mo	NR[c]	Age: <12 y
Healy et al. (2013) (31)	Retrospective case review	16	Unknown	3-y review	9 (56)	Age: <12 y
Terra et al. (2014) (32)	Retrospective case-control[d]	36	Mixed	3-y review	VNS group: 20 (55.4)	Age: <18 y Difference from baseline seizure frequency[e]
Yu et al. (2014) (33)	Retrospective case review	69/252[f]	Mixed	12 mo	28 (40.6)	Age: <12 y
Maleknia et al. (2023) (34)	Retrospective cohort study	45	Generalized MRE	5-y	4 (36.4) patients younger than 4 y at 6-mo, 1-, 2-, and 5-y FU; 11 (32.4) patients 4 to 6 y at 6-mo; 14 (41.2) patients 4 to 6 y at 1-y;	Age: <6 y (11 patients younger than 4 y)

					13 (38.2) patients 4 to 6 y at 2-y; and 14 (41.2) patients 4 to 6 y at 5-y	

FU: follow-up; LGS: Lennox-Gastaut syndrome; mo: month(s), MRE: medically refractory epilepsy; NR: not reported; OBS: observational; RCT: randomized controlled trial; SD: standard deviation; SFR: seizure frequency reduction; VNS: vagus nerve stimulation; y: year(s).

[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) vs. control group: 83.63 (SD=41.43).

[f] Sixty-nine of 252 of identified cases had evaluable pre- and postimplantation data.

Section Summary: Treatment-Resistant Seizures

The evidence on the efficacy of VNS for treatment of medically refractory seizures consists of 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 VNS in individuals with treatment-resistant depression is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

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.

For treatment-resistant depression, additional therapy such as adding a different class of medication or adding psychotherapy, switching to a different therapy such as a different antidepressant or electroconvulsive therapy are practices that may be used.

Outcomes
For treatment-resistant depression, the outcomes of interest are depression symptoms as measured by the Montgomery-Asberg Depression Rating Scale (MADRS) 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, MADRS, 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).

<u>Study Selection Criteria</u>
Methodologically credible studies were selected using the following principles:

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

Systematic Reviews

Several systematic reviews and meta-analyses have assessed the role of VNS in treatment-resistant depression. A 2008 systematic review of the literature for VNS of treatment-resistant depression identified 1 randomized trial. (35) VNS was found to be associated with a reduction in depressive symptoms in the open-label studies. However, results from the only double-blind trial were considered inconclusive. (36, 37) Daban et al. (2008) concluded that further clinical trials are needed to confirm efficacy of VNS in treatment-resistant depression. (35)

In a meta-analysis that included 14 studies, Martin and Martin-Sanchez (2012) reported that, among the uncontrolled studies included in their analysis, 31.8% of subjects responded to VNS treatment. (38) However, results from a meta-regression to predict each study's effect size suggested that 84% of the observed variation across studies was explained by baseline depression severity. Berry et al. (2013) (39) reported on results from a meta-analysis of 6 industry-sponsored studies of safety and efficacy for VNS in treatment-resistant depression, which included the D-01, D-02, D-03 (Bajbouj et al. [2010]), (40) D-04, and D-21 (Aaronson et al. [2013]) (41) study results. Also, the meta-analysis used data from a registry of patients with treatment-resistant depression (335 patients receiving VNS plus treatment as usual and 301 patients receiving treatment as usual only) that were unpublished at the time of the meta-analysis publication (NCT00320372). The authors reported that adjunctive VNS was associated with a greater likelihood of treatment response (odds ratio [OR], 3.19; 95% confidence interval [CI], 2.12 to 4.66). However, the meta-analysis did not have systematic study selection criteria, limiting the conclusions that can be drawn from it.

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. (42) 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

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). (36) 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 IDS 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).

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). (41) 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% of patients, 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.

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. (43, 37) 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. (44) 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.

Aaronson et al. (2017) reported on results from the FDA required post-marketing surveillance study, which was a 5-year, prospective, open-label, nonrandomized observational study of the Treatment-Resistant Depression Registry. (45) The study compared treatment as usual, with or without adjunctive VNS. It was conducted at 61 sites in the United States and included 795 patients (VNS n=494, no VNS n=301) who were experiencing a major depressive episode (unipolar or bipolar depression) of at least 2 years' duration or had a history of 3 or more depressive episodes (including the current episode), and who had failed at least 4 prior depression treatments (including electroconvulsive therapy). Study treatment was patient-

selected and/or assigned on an individualized basis at the discretion of the study site. The exception was for a subset of 159 (32%) VNS patients who were rolled over from the D-21 study (described above). (41) The primary efficacy outcome was the cumulative first-time 5-year response rate, defined as at least a 50% reduction in the MADRS score at any post-baseline visit. Due to its nonrandomized design, several significant between-groups differences were noted at baseline, including that the VNS group had a higher rate of past treatment with electroconvulsive therapy (57% vs. 40%; p<.001), a higher number of prior failed depression treatments (8.2 vs. 7.3; p=.010), more psychiatric hospitalizations within the 5 years before enrollment (3.0 vs. 1.9; p<.001) and lifetime suicide attempts (1.8 vs. 1.2; p=.02), and a higher mean MADRS score (33.1 vs. 29.3; p<.001). The propensity score method was used to adjust for these baseline imbalances. Clinical outcomes were significantly improved in the VNS groups, including higher cumulative first-time response (67.6% vs. 40.9%; p<.001) and cumulative first-time remission (MADRS total score ≤ 9 at any postbaseline visit, 43.3% vs. 25.7%; p<.001). The VNS arm also demonstrated a significantly greater reduction in suicidality on 2 of 3 different measures: Quick Inventory of Depressive Symptomatology–Self Report (QIDS-SR) item 12 (OR=2.11; 95% CI, 1.28 to 3.48), investigator-completed suicidality assessment (OR=2.04; 95% CI, 1.08 to 3.86), but not MADRS item 10 (OR=1.67; 95% CI, 0.98 to 2.83). There was no significant difference between the VNS and no VNS groups in completed suicides (1.01 per 1,000 person-years [95% CI, 0.11 to 3.64] and 2.20 per 1,000 person-years [95% CI, 0.24 to 7.79], respectively). Important limitations of the study include lack of a sham condition and the potential for bias due to confounding from unrestricted and uncontrolled concomitant treatments and bias in outcome measurement, which was unblinded. Additionally, other important outcomes such as quality of life and relapse were not reported.

McAllister-Williams et al. (2020) (46) 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]). (45) 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.

Case Series

Several case series published before the randomized trials showed rates of improvement with VNS, as measured by a 50% improvement in depression score, of 31% at 10 weeks to greater than 40% at 1 to 2 years, but there were some losses to follow-up. (14, 47, 48) Natural history,

placebo effects, and patient and provider expectations make it difficult to infer efficacy from case series data.

Other case series do not substantially strengthen the evidence supporting VNS. A case series by Bajbouj et al. (2010), which followed patients for 2 years, showed that 53.1% (26/49) met criteria for treatment response and 38.9% (19/49) met criteria for remission. (40) A small 2008 study of 9 patients with rapid-cycling bipolar disorder showed improvements in several depression rating scales over 40 weeks of observation. (49) In a 2014 case series that included 27 patients with treatment-resistant depression, 5 patients demonstrated complete remission after 1 year, and 6 patients were considered responders. (50)

Adverse events of VNS therapy included voice alteration, headache, neck pain, and cough, which are known from prior experience with VNS therapy for seizures. Regarding specific concerns for depressed patients (e.g., those with mania, hypomania, suicide, or worsening depression), there does not appear to be a greater risk of these events during VNS therapy. (37)

Section Summary: Treatment-Resistant Depression

There are 2 RCTs evaluating the efficacy of implanted 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. Another neuromodulation technique (transcranial magnetic stimulation) for the treatment of depression is evaluated in medical policy PSY301.015.

Treatment of Chronic Heart Failure

Clinical Context and Therapy Purpose

The purpose of implantable VNS in individuals with chronic heart failure is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

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.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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

Systematic Reviews
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. (51) 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 Table 9. The meta-analysis found significant improvements in New York Heart Association (NYHA) 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 (Table 10).

Table 9. Characteristics of Systematic Reviews of Implantable VNS for Chronic Heart Failure

Study	Dates	Trials	Participants	N (Range)	Design	Duration

Sant'Anna et al. (2021) (51)	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

Table 10. Results of Systematic Reviews of RCTs of Implantable VNS for Chronic Heart Failure

Study	Improvement in NYHA functional class	Quality of Life[a]	6-minute walk test	NT-proBNP levels	Mortality
Sant'Anna et al. (2021) (51)					
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; 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

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 NYHA class quality of life, 6-minute walk test, and left ventricular (LV) ejection fraction. (44) 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). (52) 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. (53) 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).

Kumar et al. (2023) published a case series in patients with heart failure with preserved ejection fraction (HFpEF) or mildly reduced ejection fraction (HFmrEF), called the ANTHEM-HFpEF trial. (54) Fifty-two patients with HFpEF or HFmrEF, NYHA class II to III on guideline-directed medical therapy were successfully implanted with VNS therapy. At 12 months, NYHA class improved in 55% of patients (<0.0001), 6 minute walk test distance improved (mean, 300 m ± 71 at 12 mo vs 288 m ± 78 m at baseline; p<.05), and quality of life scores were improved compared to baseline (p<.0001).

Section Summary: Treatment of Chronic Heart Failure

The evidence on VNS for treatment of chronic heart failure consists of a systematic review including 4 RCTs and 3 uncontrolled studies. A meta-analysis of 4 RCTs found significant improvements in NYHA 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, NYHA class, 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 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.

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

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.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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

Systematic Reviews
Ramos-Castaneda et al. (2022) published a systematic review evaluating VNS on upper limb motor recovery after stroke. (55) Three RCTs by Dawson et al. and Kimberley et al, which are summarized in the section below, were pooled for the analysis evaluating the role of implanted VNS. Results demonstrated that implanted VNS improved upper limb motor function based on Fugl-Meyer Assessment-Upper Extremity (FMA-UE) score when compared to control (mean difference=2.78; 95% CI, 1.38 to 4.18).

Randomized Controlled Trials
Dawson et al. (2016) conducted a randomized pilot trial of VNS in patients with upper-limb dysfunction after ischemic stroke. (56) 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.). (57) 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 FMA-UE 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 pilot sham-controlled RCT in 17 patients (VNS, n=8 and sham VNS, n=9) with arm weakness after ischemic stroke. (58) The mean FMA-UE 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 FMA-UE 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: Treatment of Upper-Limb Impairment Due to Stroke

The evidence on VNS for treatment of upper-limb impairment due to stroke consists of 3 small RCTs and a systematic review that pooled their data. 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. The systematic review found that implanted VNS improved upper limb motor function based on FMA-UE score when compared to control.

Other Neurologic Conditions (Essential Tremor, Headache, Fibromyalgia, Tinnitus, and Autism)

Clinical Context and Therapy Purpose

The purpose of implantable 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.

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

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.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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

VNS has been investigated with small pilot studies or studies evaluating the mechanism of disease for several conditions. These conditions include essential tremor, (20) fibromyalgia, (59), and tinnitus. (60) The utility of VNS added to behavioral management of autism and autism spectrum disorders has been posited, but there are no RCTs. (61) None of these studies are sufficient to draw conclusions on the effect of VNS on these conditions.

Section Summary: Other Neurologic Conditions (Essential Tremor, Headache, Fibromyalgia, Tinnitus, and Autism)
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.

TRANSCUTANEOUS VAGUS NERVE STIMULATION
Prevention of Cluster Headaches
Clinical Context and Therapy Purpose
The purpose of noninvasive vagus nerve stimulation (nVNS) or transcutaneous vagus nerve stimulation (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.

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

Populations
The relevant population of interest is individuals with cluster headache, using nVNS for prevention. The International Headache Society's (IHS) International Classification of Headache

Disorders classifies types of primary and secondary headaches. (62) 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 (62) 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 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.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Only conditions for which there is at least 1 RCT assessing the use of tVNS are discussed because case series are inadequate to determine the effect of the technology.

Randomized Controlled Trials

One RCT has evaluated nVNS for prevention of cluster headache compared to standard care. Characteristics of the trial are shown in Table 11. Results are shown in Table 12.

Table 11. Characteristics of RCTs of nVNS for Prevention of Cluster Headache

						Interventions	
Author (year); Trial	**Countries**	**Sites**	**Dates**	**Participants**	**Randomized treatment period**	**Active**	**Comparator**
Gaul et al. (2016, 2017) (63, 64); PREVA	Germany, United Kingdom, Belgium, Italy	10	2012 to 2014	18 to 70 years of age, cCH diagnosis	4 weeks	n=48; nVNS + SOC	n=49; SOC

cCH: chronic cluster headache; nVNS: noninvasive vagus nerve stimulation; PREVA: PREVention and Acute treatment of chronic cluster headache; RCT: randomized controlled trial; SOC: standard of care.

Gaul et al. (2016) reported on the results of a randomized open-label study of tVNS for the prevention of chronic cluster headache. (63) Forty-eight patients with chronic cluster headache were randomized to tVNS or individualized SOC. tVNS 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 (e.g., attack frequency reductions of ≥25%, ≥75%, or ≥100 from baseline). Response consistently favored nVNS regardless of definition. (64)

Table 12. Results of RCTs of nVNS for Prevention of Cluster Headache

Author (year); Study	Response (%)	Other efficacy outcomes		Quality of life or functional outcomes	Adverse events
	≥50% reduction in mean number of attacks (%)	Attack reduction from baseline per week (mean)	Acute medication use	EQ-5D-3L	≥1 Adverse event
Gaul et al. (2016, 2017) (63, 64); PREVA (NCT01701245)				Change from baseline	
n	93	93	Unclear	81	97
nVNS	40%	-5.9	-15	0.15	52%
SOC	8%	-2.1	-2	-0.05	49%
Treatment effect (95% CI)	NR; p<0.01	3.9 (0.5 to 7.2); p=0.02	NR	Difference=0.19 (0.05 to 0.33); p<0.01	

CI: confidence interval; EQ-5D-3L: European Quality of Life 5 Dimensions 3 Level Version; NR: not reported; nVNS: noninvasive transcutaneous vagus nerve stimulation; PREVA: PREVention and Acute treatment of chronic cluster headache; RCT: randomized controlled trial; SOC: standard of care.

Relevance and design and conduct limitations are shown in Tables 13 and 14. The PREVA prevention study was not blinded and had no sham nVNS. The double-blind, study treatment period was less than 1 month, which limits inference about continued response.

Table 13. Study Relevance Limitations of RCTs of nVNS for Prevention of Cluster Headache

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Gaul et al. (2016, 2017) (63, 64); PREVA	2. Study population unclear				1: 4-week tx period, cannot assess

					continued response

nVNS: noninvasive transcutaneous vagus nerve stimulation; PREVA: PREVention and Acute treatment of chronic cluster headache; RCT: randomized controlled trial; tx: treatment.
The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 14. Study Design and Conduct Limitations of RCTs of nVNS for Prevention of Cluster Headache

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Gaul et al. (2016, 2017) (63, 64); PREVA		1: No blinding		1: Differential rate of missing data for quality of life measures (higher missing in nVNS)		

nVNS: noninvasive vagus nerve stimulation; PREVA: PREVention and Acute treatment of chronic cluster headache; RCT: randomized controlled trial.
The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

The PREVA RCT also provided results from a 4-week open-label period. Results are shown in Table 15.

Table 15. Extended, Open-Label Follow-up of nVNS Patients From PREVA RCT

Author (year); Study	Response (%)	Attack frequency
	≥50% reduction in mean number of attacks (%)	Attack reduction from randomized phase per week (mean)
Gaul et al. (2016, 2017) (63, 64); PREVA		
n	45	30
4 week follow-up	29%	2

nVNS: noninvasive vagus nerve stimulation; PREVA: PREVention and Acute treatment of chronic cluster headache; RCT: randomized controlled trial.

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 VNS for Prevention of Cluster Headaches

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 European Quality of Life 5 Dimensions 3 Level Version. 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.

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

Populations

The relevant population of interest is individuals with cluster headache, using nVNS for treatment. The IHS International Classification of Headache Disorders classifies types of primary

and secondary headaches. (62) 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 (62) 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 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. (65) 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.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Only conditions for which there is at least 1 RCT assessing the use of tVNS are discussed because case series are inadequate to determine the effect of the technology.

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. Characteristics of the trials are shown in Table 16. Results are shown in Table 17.

Table 16. Characteristics of RCTs of nVNS for Treatment of Cluster Headache

						Interventions	
Author (year); Trial	**Countries**	**Sites**	**Dates**	**Participants**	**Randomized treatment period**	**Active**	**Comparator**
Silberstein et al. (2016) (66); ACT1	U.S.	20	2013 to 2014	18 to 75 years of age, eCH or cCH	Up to 1 month	n=73; nVNS	n=77; Sham

				diagnosis (3.3% Asian, 8% Black, 87.3% White, 1.4% race/ethnicity not reported)			
Goadsby et al. (2018) (67); ACT2	UK, Denmark, Germany, Netherlands	9	2013 to 2014	18 or older years of age; eCH or cCH diagnosis (99% White, 1% Asian)	2 weeks	n=50; nNVS	n=52; Sham

ACT1: Non-invasive Neurostimulation of the Vagus Nerve With the GammaCore Device for the Treatment of Cluster Headache; ACT2: A Randomized, Multicentre, Double-blind, Parallel, Sham-controlled Study of GammaCore®, a Non-invasive Neurostimulator Device for the Acute Relief of Episodic and Chronic Cluster Headache; cCH: chronic cluster headache; eCH: episodic cluster headache; nVNS: noninvasive vagus nerve stimulation; RCT: randomized controlled trial.

Silberstein et al. (2016) reported on the results of a randomized, double-blind, sham-controlled study (ACT1) for treatment of acute cluster headache attacks. (66) 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.

Goadsby et al. (2018) reported on the results of randomized, double-blind, sham-controlled study (ACT2) for the treatment of acute cluster headache attacks. (67) 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).

de Coo et al. (2019) combined the data from ACT1 and ACT2 meta-analytically for the 2 primary outcomes reported in the 2 studies. (68) The authors reported an interaction between treatment group and cluster headache subtype in the pooled analysis (p<.05 for both outcomes).

Table 17. Results of RCTs of nVNS for Treatment of Cluster Headache

Author (year); Study	**Response (%)**	**Other efficacy outcomes**			**Quality of life or functional outcomes**	**Adverse events**
	Response (%)	**Pain-free at 15 min (%)**	**Sustained response (%)**			**Adverse events (%)**
Silberstein et al. (2016) (66); ACT1	First attack; Pain intensity score of 0 or 1 on a 5-point scale at 15 min	≥50% of attacks	Through 60 minutes	Rescue medication use	Quality of life or functional outcome	≥1 Adverse event
Overall						
n	133	133	133	133	NR	150
nVNS	27%	12%	27%	38%		25%
Sham	15%	7%	12%	51%		40%
Treatment effect (95% CI)	NR; p=0.10	NR; p=0.33	NR; p=0.04	NR; p=0.15		
By subgroup						
Treatment by subgroup interaction p-value	NR	NR	NR	NR		
cCH subgroup						
n	48	48	48	48	NR	
nVNS	14%	5%	14%	32%		
Sham	23%	15%	15%	54%		
Treatment effect	NR; p=0.48	NR; p=0.36	NR; p=1.0	NR; p=0.13		

(95% CI)						
eCH subgroup						
n	85	85	85	85	NR	
nVNS	34%	16%	34%	42%		
Sham	11%	2%	11%	49%		
Treatment effect (95% CI)	NR; p=0.01	NR; p=0.04	NR; p=0.01	NR; p=0.53		
Goadsby et al. (2018) (67); ACT2	Proportion of attacks; Pain intensity score of 0 or 1 on a 5-point scale at 30 min	Proportion of attacks				
Overall						
n	92	92	NR	NR	NR	102
nVNS	43%	14%				40%
Sham	28%	12%				27%
Treatment effect (95% CI)	NR; p=0.05	NR; p=0.71				
By subgroup						
Treatment by subgroup interaction p-value		p=0.04				
cCH subgroup						
n	66	66				
nVNS	37%	5%				
Sham	29%	13%				
Treatment effect (95% CI)	NR; p=0.34	NR; p=0.13				
eCH subgroup						
n	27	27				
nVNS	58%	48%				
Sham	28%	6%				
Treatment effect (95% CI)	NR; p=0.07	NR; p<0.01				

ACT1: Non-invasive Neurostimulation of the Vagus Nerve With the GammaCore Device for the Treatment of Cluster Headache; ACT2: A Randomized, Multicentre, Double-blind, Parallel, Sham-controlled Study of GammaCore®; a Non-invasive Neurostimulator Device for the Acute Relief of Episodic and Chronic Cluster Headache; cCH: chronic cluster headache; CI: confidence interval; eCH: episodic cluster headache; NR: not reported; nVNS: noninvasive transcutaneous vagus nerve stimulation; RCT: randomized controlled trial.

Relevance and design and conduct limitations are shown in Tables 18 and 19. The ACT1 and ACT2 treatment studies both included sham nVNS. The sham was identical in appearance, weight, visual and audible feedback, and user application and produces a low-frequency signal but did not generally cause muscle contraction. The double-blind, study treatment period was less than 1 month in both RCTs which limits inference about continued response. The ACT1 and ACT2 studies did not include quality of life or functional outcomes.

Table 18. Study Relevance Limitations of RCTs of nVNS for Treatment of Cluster Headache

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Silberstein et al. (2016) (66); ACT1	4. Enrolled populations not reflective of relevant diversity			1: No quality of life or functional outcomes reported	1: Less than 1-month tx period, cannot assess continued response
Goadsby et al. (2018) (67); ACT2	4. Enrolled populations not reflective of relevant diversity			1: No measures of sustained pain freedom, relapse or quality of life or functional outcomes reported	1: 2-week tx period, cannot assess continued response

ACT1: Non-invasive Neurostimulation of the Vagus Nerve With the GammaCore Device for the Treatment of Cluster Headache; ACT2: A Randomized, Multicentre, Double-blind, Parallel, Sham-controlled Study of GammaCore®, a Non-invasive Neurostimulator Device for the Acute Relief of Episodic and Chronic Cluster Headache; nVNS: noninvasive transcutaneous vagus nerve stimulation; RCT: randomized controlled trial; tx: treatment.
The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 19. Study Design and Conduct Limitations of RCTs of nVNS for Treatment of Cluster Headache

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Silberstein et al. (2016) (66); ACT1						3: Interaction p not reported for treatment by cluster headache subtype
Goadsby et al. (2018) (67); ACT2				1: Differential rate of return of diaries in tx groups (4% missing in nVNS vs. 12% missing in sham)		

ACT1: Non-invasive Neurostimulation of the Vagus Nerve With the GammaCore Device for the Treatment of Cluster Headache; ACT2: A Randomized, Multicentre, Double-blind, Parallel, Sham-controlled Study of GammaCore®, a Non-invasive Neurostimulator Device for the Acute Relief of Episodic and Chronic Cluster Headache; nVNS: noninvasive vagus nerve stimulation; RCT: randomized controlled trial; tx: treatment.
The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

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

The RCTs also provided results from open-label periods during which patients received nVNS ranging from 2 weeks in ACT2 to 3 months in ACT1. Patients continued to respond to nVNS during the open-label period. Results are shown in Table 20.

Table 20. Extended, Open-Label Follow-up of nVNS Patients From RCTs

Author (year); Study	**Response (%)**	**Attack frequency**
	Response (%)	**Pain-free at 15 min (%)**
Silberstein et al. (2016) (66); ACT1	**First attack; Pain intensity score of 0 or 1 on a 5-point scale at 15 min**	**≥50% of attacks**
Overall		
n	NR	NR
3-month follow-up		
cCH subgroup		
n	48	NR
3-month follow-up	35% (95% CI, 22 to 51%)	
eCH subgroup		
n	85	NR
3-month follow-up	29% (95% CI, 20 to 40)	
Goadsby et al. (2018) (67); ACT2	**Proportion of attacks; Pain intensity score of 0 or 1 on a 5-point scale at 30 min**	**Proportion of attacks**
Overall		
n	NR	83
2-week follow-up		14% (95% CI NR)
cCH subgroup		
n	NR	58
2-week follow-up		11% (95% CI NR)
eCH subgroup		
n	NR	25
2-week follow-up		26% (95% CI NR)

ACT1: Non-invasive Neurostimulation of the Vagus Nerve With the GammaCore Device for the Treatment of Cluster Headache; ACT2: A Randomized, Multicentre, Double-blind, Parallel, Sham-controlled Study of GammaCore®, a Non-invasive Neurostimulator Device for the Acute Relief of Episodic and Chronic Cluster Headache; cCH: chronic cluster headache; CI: confidence interval; eCH: episodic cluster headache; NR: not reported; nVNS: noninvasive vagus nerve stimulation; RCT: randomized controlled trial.

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 VNS for Treatment of Cluster Headaches

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 Migraine 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 migraine headaches as an alternative to standard care and to reduce the frequency of attacks for migraine as an adjunct to standard care.

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

Populations

The relevant population of interest is individuals with migraine headache, using nVNS for treatment. The IHS International Classification of Headache Disorders classifies types of primary and secondary headaches. (62) 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 (62): 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. (65) 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.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Only conditions for which there is at least 1 RCT assessing the use of tVNS are discussed because case series are inadequate to determine the effect of the technology.

One RCT has evaluated nVNS for treatment of acute migraine headache compared to sham nVNS. Characteristics of the trial are shown in Table 21. Results are shown in Table 22. Relevance and design and conduct limitations are in Tables 23 and 24.

Table 21. Characteristics of RCTs of nVNS for Migraine Treatment

					Interventions	
Author (year); Trial	**Countries**	**Sites**	**Dates**	**Participants**	**Active**	**Comparator**
Tassorelli (2018) (69), Grazzi (2018) (70), Martelletti (2018) (71); PRESTO (NCT02686034)	Italy	10	2016 to 2017	18 to 75 years of age, migraine diagnosis with or without aura; 3 to 8 attacks/month; <15 headache days/month over last 6 months (100% White)	n=122; nVNS	n=126; Sham nVNS

nVNS: noninvasive vagus nerve stimulation; PRESTO: A Prospective, Multi-centre, Randomized, Double-blind, Sham-controlled Study of gammaCore® Non-invasive Vagus Nerve Stimulator (nVNS), for the Acute Treatment of Migraine; RCT: randomized controlled trial.

A Prospective, Multi-centre, Randomized, Double-blind, Sham-controlled Study of gammaCore® Non-invasive Vagus Nerve Stimulator (nVNS) for the Acute Treatment of Migrane (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. (69) 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 minutes 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.

Table 22a. Results of RCTs of nVNS for Migraine Treatment

Author (year); Study	**Pain-relief (%)**	**Pain-free (%)**	**Response over multiple attacks (%)**
Tassorelli (2018) (69), Grazzi (2018) (70), Martelletti (2018) (71); PRESTO (NCT02686034)	Decrease in pain intensity from moderate (2) or severe (3) to mild (1) or no (0) pain on a 4-point scale at 120 minutes, first attack	Pain-free without using rescue medication at 120 minutes, first attack	Pain-free at 120 minutes for ≥50% of their attacks
n	243	243	243
nVNS	41%	22%	32%
Sham	28%	13%	18%
Treatment effect (95% CI)	Difference=13% (NR); p=0.03	Difference=11% (NR); p=0.07	Difference=14% (NR); p=0.02

CI: confidence interval; nVNS: noninvasive vagus nerve stimulation; NR: not reported;
PRESTO: A Prospective, Multi-centre, Randomized, Double-blind, Sham-controlled Study of gammaCore® Non-invasive Vagus Nerve Stimulator (nVNS,) for the Acute Treatment of Migraine; RCT: randomized controlled trial.

Table 22b. Results of RCTs of nVNS for Migraine Treatment

Author (year); Study	Sustained response/ Relapse or recurrence over 48 hours	Rescue medication use	QOL or functional outcomes	Adverse events (%)
Tassorelli (2018) (69), Grazzi (2018) (70), Martelletti (2018) (71); PRESTO (NCT02686034)	Sustained pain-free response at 48 hours, first attack	Did not Require rescue medication (%)		≥1 Adverse event
n	62	243	NR	248
nVNS	58%	59%		18%
Sham	69%	42%		18%
Treatment effect (95% CI)	NR; p=0.38	NR; p=0.01		

CI: confidence interval; nVNS: noninvasive vagus nerve stimulation; NR: not reported; PRESTO: A Prospective, Multi-centre, Randomized, Double-blind, Sham-controlled Study of gammaCore® Non-invasive Vagus Nerve Stimulator (nVNS,) for the Acute Treatment of Migraine; QOL: quality of life; RCT: randomized controlled trial.

Table 23. Study Relevance Limitations of RCTs of nVNS for Treatment of Migraine Headache

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Tassorelli (2018) (69); PRESTO	4. Enrolled populations not reflective of relevant diversity			1: No quality of life or functional outcomes reported	1: 4-week tx period, cannot assess continued response

nVNS: noninvasive vagus nerve stimulation; PRESTO: A Prospective, Multi-centre, Randomized, Double-blind, Sham-controlled Study of gammaCore® Non-invasive Vagus Nerve Stimulator (nVNS,) for the Acute Treatment of Migraine; RCT: randomized controlled trial; tx: treatment

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

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

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

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. the intervention of interest.

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

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 24. Study Design and Conduct Limitations of RCTs of nVNS for Treatment of Migraine Headache

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Tassorelli (2018) (69); PRESTO						

nVNS: noninvasive vagus nerve stimulation; PRESTO: A Prospective, Multi-centre, Randomized, Double-blind, Sham-controlled Study of gammaCore® Non-invasive Vagus Nerve Stimulator (nVNS), for the Acute Treatment of Migraine; RCT: randomized controlled trial.
The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

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. (72)

Section Summary: Transcutaneous VNS for Migraine Headaches

One RCT has evaluated nVNS for the acute treatment of migraine 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 minutes 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 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 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.

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

Populations

The relevant population of interest is individuals with migraine headache, using nVNS for prevention. The IHS International Classification of Headache Disorders classifies types of primary and secondary headaches. (62) 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 (62): 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 IHS 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.

<u>Study Selection Criteria</u>
Methodologically credible studies were selected using the following principles:

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

Only conditions for which there is at least 1 RCT assessing the use of tVNS are discussed because case series are inadequate to determine the effect of the technology.

Three RCTs have evaluated nVNS for prevention of migraine headache compared to sham. Characteristics of the trial are shown in Table 25. Results are shown in Table 26. Relevance and design and conduct limitations are in Tables 27 and 28.

Table 25. Characteristics of RCTs of nVNS for Migraine Prevention

					Interventions	
Author (year); Trial	**Countries**	**Sites**	**Dates**	**Participants**	**Active**	**Comparator**
Silberstein et al. (2016) (73); EVENT (NCT01667250)	U.S.	6	2012 to 2014	18 to 65 years of age, chronic migraine diagnosis with or without aura; <15 headache days/month over last 3 months (86.4% White, 5.1% Black, 8.5% race/ethnicity not reported)	n=30; nVNS	n=29 sham nVNS
Diener et al. (2019) (74); PREMIUM (NCT02378844)	Belgium, Denmark, Germany, Greece, Netherlands, Norway, Spain, U.K.	22	2015 to 2017	18 to 75 years of age, migraine diagnosis with or without aura, 5–12 migraine days per month over past 4 months with at least 2 migraines lasting more than 4 hours (94.9% White, 5.1% race/ ethnicity not reported)	n=169 nVNS	n=172 sham nVNS
Najib et al. (2022) (75); PREMIUM II	U.S.	27	2018 to 2020	18 to 75 years of age; episodic or chronic migraine with or without	n=114 nVNS	n=117 sham

				aura; 8 to 20 headache days per month over past 3 months with at least 5 of the days being migraine days (migraines lasting more than 4 hours or treated with migraine-specific treatment); (>91% White patients enrolled)		

EVENT: Non-Invasive Neurostimulation of the Vagus Nerve with the GammaCore Device, for the Prevention of Chronic Migraine; nVNS: noninvasive vagus nerve stimulation; PREMIUM: A Randomized, Multicentre, Double-blind, Parallel, Sham-controlled Study of gammaCore®, a Non-invasive Vagal Nerve Stimulator (nVNS) for Prevention of Episodic Migraine; PREMIUM II: A Randomized, Multicenter, Double-blind, Parallel, Sham-controlled Study of Non-invasive Vagus Nerve Stimulation for the Prevention of Migraines; RCT: randomized controlled trial.

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. (73) 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. (74) 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. Results showed 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 in the intention-to-treat (ITT) population.

The PREMIUM II trial was a multicenter, sham-controlled RCT conducted in several U.S. sites and included patients who experienced 8 to 20 headache days per month with at least 5 of the days being migraine days. (75) The study included a 4-week run-in period during which no

treatment was administered (N=336). After the run-in period, 231 patients were randomly assigned to receive nVNS (n = 114) or sham (n = 117) therapy during the double-blind period and were part of the ITT population (i.e., had ≥1 study treatment during the double-blind phase). The COVID-19 pandemic led to an early termination of this trial, therefore, the population was approximately 60% smaller than the statistical target for full power. The modified ITT (mITT) population, which included those who were at least 66% adherent to treatment during the double-blind phase, included 56 patients in the nVNS group and 57 in the sham group. Results showed that in the mITT population, nVNS was not statistically significantly superior to sham with respect to the primary outcome of reduction in the number of migraine days per month during weeks 9 through 12 (mean difference=-0.83 days; p=.2329), nor other outcomes such as mean change in the number of headache days or acute medication days. However, in the mITT population, the percentage of patients with at least a 50% reduction in the number of migraine days was significantly greater in the nVNS group (44.87%) than in the sham group (26.81%; p=.048). Furthermore, nVNS was significantly better than sham at decreasing headache impact, as measured by the Headache Impact Test-6 (HIT-6), and at decreasing migraine-related disability, as measured by the Migraine Disability Assessment Scale (MIDAS).

Table 26. Results of RCTs of nVNS for Migraine Prevention

Author (year); Study	**Response (%)**	**Frequency of headache**	**Other medication use**	**Quality of life or functional outcomes**	**Adverse events (%)**
Silberstein et al. (2016) (73): EVENT (NCT01667250)	≥50% reduction in number of headache days	Change from baseline in number of headache days / 28 days	Acute medication		≥1 Adverse event
n	59	59	59	NR	59
nVNS	10%	-1.4	NR		57%
Sham	0%	-0.2	NR		55%
Treatment effect (95% CI)	NR	NR; p=0.56	NR; "Comparable"		NR
Diener et al. (2019) (74); PREMIUM (NCT02378844)	Reduction of at least 50% from baseline to the last 4 weeks	Reduction in number of migraine days from baseline to the last 4 weeks (Mean days)	Acute medication days		≥1 Adverse event

n	332	332	332	NR	341
nVNS	32%	-2.3	-1.9		44%
Sham	25%	-1.8	-1.4		53%
Treatment effect (95% CI)	Odds Ratio= 1.40 (0.85, 2.32); p=0.19	Difference=-0.47 (CI NR); p=0.15	p=0.11		
Najib et al. (2022) (75); PREMIUM II	≥50% reduction in number of headache days	Mean change in number of migraine days	Acute medication days	Mean change in HIT-6 score	
N	113	113	113	108	
nVNS	44.87%	-3.12	-2.53	-4.9	
Sham	26.81%	-2.29	-1.36	-2.3	
Treatment effect (95% CI)	OR=2.22 (CI NR); p=.0481	Difference=-0.83 (CI NR); p=.2329	Difference=-1.17 (CI NR); p=.1132	Difference=-2.6 (CI NR); p=.0250	
		Mean change in number of headache days		MIDAS shift from moderate/severe to none/mild	
N		113		88	
nVNS		-4.56		25%	
Sham		-3.00		9.1%	
Treatment effect (95% CI)		Difference=-1.56 (CI NR); p=.0530		15.9% (CI NR); p=.0472	

CI: confidence interval; EVENT: Non-Invasive Neurostimulation of the Vagus Nerve With the GammaCore Device, for the Prevention of Chronic Migraine; HIT-6: Headache Impact Test-6; MIDAS: Migraine Disability Assessment; NR: not reported; nVNS: noninvasive vagus nerve stimulation; OR: odds ratio; PREMIUM: A Randomized, Multicentre, Double-blind, Parallel, Sham-controlled Study of gammaCore®, a Non-invasive Vagal Nerve Stimulator (nVNS), for Prevention of Episodic Migraine; PREMIUM II: A Randomized, Multicenter, Double-blind, Parallel, Sham-controlled Study of Non-invasive Vagus Nerve Stimulation for the Prevention of Migraines; RCT: randomized controlled trial.

Table 27. Study Relevance Limitations of RCTs of nVNS for Prevention of Migraine Headache

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]

Silberstein et al. (2016) (73); EVENT (NCT01667250)	4. Enrolled populations not reflective of relevant diversity	5: ~20% of participants discontinued tx during first 2 month	2: Sham did not deliver electrical stimulations, may have compromised blinding 4: ~20% of participants discontinued tx during first 2 months	1: No quality of life or functional outcomes reported	1: 2-month tx period, cannot assess continued response
Diener et al. (2019) (74); PREMIUM (NCT02378844)	4. Enrolled populations not reflective of relevant diversity			1: No quality of life or functional outcomes reported	1: 12-week double-blind tx period, cannot assess continued response
Najib et al. (2022) (75); PREMIUM II	4. Enrolled populations not reflective of relevant diversity		1. Not clearly defined; unclear if sham device delivered electrical stimulations		1: 12-week double-blind tx period, cannot assess continued response

EVENT: Non-Invasive Neurostimulation of the Vagus Nerve With the GammaCore Device, for the Prevention of Chronic Migraine; nVNS: noninvasive vagus nerve stimulation; PREMIUM: A Randomized, Multicentre, Double-blind, Parallel, Sham-controlled Study of gammaCore®, a Non-invasive Vagal Nerve Stimulator (nVNS), for Prevention of Episodic Migraine; PREMIUM II: A Randomized, Multicenter, Double-blind, Parallel, Sham-controlled Study of Non-invasive Vagus Nerve Stimulation for the Prevention of Migraines; RCT: randomized controlled trial; tx: treatment.

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

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

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest; 5: Not delivered effectively

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

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 28. Study Design and Conduct Limitations of RCTs of nVNS for Prevention of Migraine Headache

Study	Allo-cation[a]	Blinding[b]	Selective Reporting[c]	Data Complete-ness[d]	Power[e]	Statistical[f]
Silberstein et al. (2016) (73); EVENT					1,2,3: No formal sample size calculations or efficacy hypotheses; primarily a feasibility RCT. Probably low power to detect difference in efficacy outcomes	
Diener et al. (2019) (74); PREMIUM (NCT02378844)						
Najib et al. (2022) (75); PREMIUM II				6. Not intent to treat analysis due to early trial termination		

EVENT: Non-Invasive Neurostimulation of the Vagus Nerve With the GammaCore Device, for the Prevention of Chronic Migraine; nVNS: noninvasive vagus nerve stimulation; RCT: randomized controlled trial; PREMIUM: A Randomized, Multicentre, Double-blind, Parallel, Sham-controlled Study of gammaCore®, a Non-invasive Vagal Nerve Stimulator (nVNS), for Prevention of Episodic Migraine; PREMIUM II: A Randomized, Multicenter, Double-blind, Parallel, Sham-controlled Study of Non-invasive Vagus Nerve Stimulation for the Prevention of Migraines; RCT: randomized controlled trial.
The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

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. (76)

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). (77)

Section Summary: Transcutaneous VNS for Prevention of Migraine Headaches

Three 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. The PREMIUM II trial was a multicenter, sham-controlled RCT including 231 randomized participants with a 12-week double-blind treatment period. Results demonstrated that treatment with nVNS was not statistically significantly superior to sham with respect to the primary outcome of reduction in the number of migraine days per month during weeks 9

through 12, nor other outcomes such as mean change in the number of headache days or acute medication days. However, the percentage of participants with at least a 50% reduction in the number of migraine days was significantly greater in the nVNS group than in the sham group. However, interpretation of these findings is limited as it was based on a mITT population of 49% of randomized patients (n=113 of original 231 participants) due to COVID-19 pandemic-related early termination.

Other Neurologic, Psychiatric, or 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.

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

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 other neurologic, psychiatric, or metabolic disorders.

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.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs or systematic reviews of RCTs.

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

Only conditions for which there is at least 1 RCT assessing the use of tVNS are discussed because case series are inadequate to determine the effect of the technology.

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) (78-80) of tVNS for the treatment of drug-resistant epilepsy. (81) 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 tVNS (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 tVNS 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). Another RCT by Yang et al. (2023), published after the meta-analysis, found similar results. (82) In total, 150 patients with drug-resistant epilepsy were randomized to tVNS (n=100) or sham VNS (n=50). The patient's current antiepileptic drugs were unchanged throughout the study. At 20 weeks of treatment, investigators found that response to treatment (experiencing ≥50% reduction in mean seizure frequency) was significantly higher with tVNS (44.74%) compared to sham (16.67%; p<.05). However, there were no significant differences in quality of life scores between groups. These results are limited by the small sample size and high dropout rate (25.3%).

Psychiatric Disorders

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. (83) 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.

Hasan et al. (2015) reported on a randomized trial of tVNS for the treatment of schizophrenia. (84) 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 (85) Reviewers also included a fifth study in a data table, although not in their text or a reference list (Hein et al. [2013] [83]; previously described). Overall, the studies assessed were limited by small size and poor generalizability.

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. (86) 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).

Treatment of Upper-Limb Impairment Due to Stroke

A systematic review by Ramos-Castaneda et al. (2022) was introduced above for implanted VNS in stroke and included both implanted and nVNS. (55) An RCT by Wu et al., which is described below, in addition to 2 other small RCTs were pooled for the analysis comparing nVNS to control in patients with upper limb impairment due to stroke (total n=64). Results demonstrated that nVNS did not significantly improve the FMA-UE score vs control (mean difference=2.15; 95% CI, -0.43 to 4.73).

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. (87) The mean FMA-UE 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 FMA-UE 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.

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). (88) 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 vs. 85 ; p=.167). An important limitation of this RCT is the lack of a sham control group.

Section Summary: Transcutaneous VNS for Other Neurologic, Psychiatric, or Metabolic Disorders.

tVNS 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 and an additional RCT, 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.

Summary of Evidence

Vagus Nerve Stimulation

For individuals who have seizures refractory to medical treatment who receive vagus nerve stimulation (VNS), the evidence includes randomized controlled trials (RCTs) and multiple observational studies. Relevant outcomes are symptoms, change in disease status, and functional outcomes. 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 an improvement in the net health outcome.

For individuals who have treatment-resistant depression who receive VNS, the evidence includes 2 RCTs evaluating the efficacy of implanted VNS for treatment-resistant depression compared to sham, 1 RCT comparing therapeutic to low-dose implanted VNS, nonrandomized comparative studies, and case series. Relevant outcomes are symptoms, change in disease status, and functional outcomes. The sham-controlled RCTs 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 and confounding biases, and lack of a control group in the case series. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have chronic heart failure who receive VNS, the evidence includes a systematic review including 4 RCTs and case series. Relevant outcomes are symptoms, change in disease status, and functional outcomes. 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%). The ANTHEM-HFpEF trial found improvements in New York Heart Association functional class, quality of life, and 6-minute walk test distances in patients with preserved ejection fraction and implanted VNS. 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 VNS, the evidence includes 3 pilot RCTs and a systematic review of these RCTs. Relevant outcomes are symptoms, change in disease status, and functional outcomes. 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. A systematic review pooling these data found that implanted VNS improved upper limb motor function based on Fugl-Meyer Assessment-Upper Extremity score when compared to control. 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. Relevant outcomes are symptoms, change in disease status, and functional outcomes. 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 (tVNS; also referred to as noninvasive VNS [nVNS]) 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. Relevant outcomes are symptoms, change in disease status, quality of life and functional outcomes. 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 minutes 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 3 RCTs. Relevant outcomes are symptoms, change in disease status, quality of life and functional outcomes. 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 PREMIUM II trial was a multicenter, sham-controlled RCT including 231 randomized participants with a 12-week double-blind treatment period. The trial was terminated early due to the COVID-19 pandemic and results were based on a modified intention-to-treat population that included 113 total participants. Results demonstrated that treatment with nVNS was not statistically significantly superior to sham with respect to the primary outcome of reduction in the number of migraine days per month during weeks 9 through 12, nor other outcomes such as mean change in the number of headache days or acute medication days. However, the percentage of patients with at least a 50% reduction in the number of migraine days was significantly greater in the nVNS group than in the sham group. 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) who receive tVNS, the evidence includes RCTs, systematic reviews of these RCTs, and case series for some of the conditions. Relevant outcomes are symptoms, change in disease status, and functional outcomes. The RCTs are all small and have various methodologic problems. None showed definitive efficacy of tVNS in improving patient outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

American Academy of Neurology

In 1999, the American Academy of Neurology released a consensus statement on the use of vagus nerve stimulation (VNS) in adults, which stated: “VNS is indicated for adults and adolescents over 12 years of age with medically intractable partial seizures who are not candidates for potentially curative surgical resections, such as lesionectomies or mesial temporal lobectomies.” (89) The guidelines were updated in 2013 and reaffirmed in 2022, stating: “VNS may be considered for seizures in children, for LGS [Lennox-Gastaut syndrome]-associated seizures, and for improving mood in adults with epilepsy (Level C). VNS may be considered to have improved efficacy over time (Level C).” (90)

American Psychiatric Association

Updated in 2010, the American Psychiatric Association guidelines for the treatment of major depressive disorder in adults included the following statement on the use of VNS: “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 [electroconvulsive

therapy],” with a level of evidence III (may be recommended on the basis of individual circumstances)." (91)

National Institute for Health and Care Excellence

In 2016, the NICE issued guidance on use of transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine (IPG552). (92) The guidance states: “Current evidence on the safety of transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine raises no major concerns. The evidence on efficacy is limited in quantity and quality.” The guidance also comments that further research is needed to clarify whether the procedure is used for treatment or prevention, for cluster headache or migraine, appropriate patient selection, and treatment regimen and suggests that outcome measures should include changes in the number and severity of cluster headache or migraine episodes, medication use, quality of life in the short and long term, side effects, acceptability, and device durability.

In 2018, the NICE also published a Medtech innovation briefing on noninvasive VNS for cluster headache (MIB162). (93) The briefing states that the "intended place in therapy would be as well as standard care, most likely where standard treatments for cluster headache are ineffective, not tolerated or contraindicated" and that key uncertainties around the evidence are that 'people with episodic and chronic cluster headaches respond differently to treatment with gammaCore. The optimal use of gammaCore in the different populations is unclear. The NICE published a Medical technologies guidance [MTG46] on gammaCore for cluster headache in December 2019. (94) The recommendations state that evidence supports using gammaCore to treat cluster headache and that gammaCore is not effective in everyone with cluster headache.

In 2020, the NICE published an Interventional Procedure Overview on implanted vagus nerve stimulation for treatment-resistant depression (IPG679). (95) The guidance states: "Evidence on the safety of implanted vagus nerve stimulation for treatment-resistant depression raises no major safety concerns, but there are frequent, well-recognized side effects. Evidence on its efficacy is limited in quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research." The guidance further states that "NICE encourages further research into implanted vagus nerve stimulation for treatment-resistant depression, in the form of randomized controlled trials with a placebo or sham stimulation arm. Studies should report details of patient selection. Outcomes should include validated depression rating scales, patient-reported quality of life, time to onset of effect and duration of effect, and any changes in concurrent treatment."

Medicare National Coverage

The Centers for Medicare & Medicaid Services (CMS) has a national coverage determination for VNS. Medicare coverage policy notes that “Clinical evidence has shown that vagus nerve stimulation is safe and effective treatment for patients with medically refractory partial onset seizures, for whom surgery is not recommended or for whom surgery has failed. Vagus nerve

stimulation is not covered for patients with other types of seizure disorders that are medically refractory and for whom surgery is not recommended or for whom surgery has failed." (96)

In response to a request from LivaNova, on May 30, 2018 CMS initiated its second reconsideration of its national coverage decision on VNS for Treatment Resistant Depression (TRD). Based on an internal literature review (search dates unspecified), CMS concluded that although the published evidence suggests that VNS is a promising treatment for patients with TRD, the reviewed studies have important flaws that leave uncertainty about its true benefits and harms. (97) Thus, effective February 15, 2019, the CMS expanded Medicare coverage to "cover U.S. Food and Drug Administration approved vagus nerve stimulation (VNS) devices for treatment resistant depression (TRD) through Coverage with Evidence Development when offered in a CMS approved, double-blind, randomized, placebo-controlled trial with a follow-up duration of at least one year with the possibility of extending the study to a prospective longitudinal study when the CMS approved, double-blind, randomized placebo-controlled trial has completed enrollment, and there are positive interim findings." CMS approval of a Coverage with Evidence Development study requires answering 9 research questions specifying measurement of response, remission, harms and other health outcome variables, use of specific eligibility criteria for TRD diagnosis as described in an Agency for Healthcare Research and Quality Technology Assessment conducted by Gaynes et al. (2018), (98) as well as 13 additional operational criteria. CMS has approved 1 ongoing study for Coverage with Evidence Development - A Prospective, Multi-center, Randomized Controlled Blinded Trial Demonstrating the Safety and Effectiveness of VNS Therapy® System as Adjunctive Therapy Versus a No Stimulation Control in Subjects With Treatment-Resistant Depression (RECOVER) (NCT03887715). (99) Conway et al. (2020) have published a detailed description of the RECOVER study rationale and design. (100)

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 29.

Table 29. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03320304[a]	A Global PRospective, Multi-cEnter, ObServational Post-markeT Study tO Assess short, Mid and Long-term Effectiveness and Efficiency of VNS Therapy® as Adjunctive Therapy in real-world patients With diFficult to Treat dEpression	500	Dec 2028
NCT03887715[a]	A Prospective, Multi-center, Randomized Controlled Blinded Trial Demonstrating the Safety and Effectiveness of VNS Therapy® System as Adjunctive Therapy Versus a No	6800	Dec 2030

	Stimulation Control in Subjects With Treatment-Resistant Depression (RECOVER)		
NCT04935567	PRediction of Vagal Nerve Stimulation EfficaCy In Drug-reSistant Epilepsy: Prospective Study for Pre-implantation Prediction	120	Dec 2026
NCT04777500	Applying Transcutaneous Auricular Vagus Nerve Stimulation to Treat Fibromyalgia	60	Mar 2023
NCT04534556	Wireless Nerve Stimulation Device To Enhance Recovery After Stroke	30	Jan 2024
NCT04448327	Sex-Dependent Impact of Transcutaneous Vagal Nerve Stimulation on the Stress Response Circuitry and Autonomic Dysregulation in Major Depression	80	Nov 2024
NCT04539964[a]	Vagus Nerve Stimulation Using the SetPoint System for Moderate to Severe Rheumatoid Arthritis: The RESET-RA Study	250	May 2027
Unpublished			
NCT02562703	Transcutaneous Vagus Nerve Stimulation for Treating Major Depressive Disorder: a Phase II, Randomized, Double-blind Clinical Trial	40	Jul 2016 (unknown)
NCT02089243	Prospective Randomized Controlled Study of Vagus Nerve Stimulation Therapy in the Patients With Medically Refractory Medial Temporal Lobe Epilepsy; Controlled Randomized Vagus Nerve Stimulation Versus Resection (CoRaVNStiR)	40	Jul 2017 (unknown)
NCT01281293[a]	A Post Market, Long Term, Observational, Multi-site Outcome Study to Follow the Clinical Course and Seizure Reduction of Patients With Refractory Seizures Who Are Being Treated With Adjunctive VNS Therapy	124	Aug 2018
NCT03380156	Effect of Transcutaneous Vagal Stimulation (TVS) on Endothelial Function and Arterial Stiffness in Patients With Heart Failure With Reduced Ejection Fraction	50	May 2020
NCT04926415	Effects of Transcutaneous Auricular Vagus Nerve Stimulation on Obesity and Insulin Resistance	30	Apr 2022

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	61885, 61886, 64553, 64568, 64569, 64570, 95971, 95976, 95977
HCPCS Codes	C1767, C1827, E0735, L8679, L8680, L8681, L8682, L8683, L8685, L8686, L8687, L8688, L8689, [Deleted 1/2024: K1020]

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been changed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
01/01/2025	Document updated with literature review. The following change was made to Coverage: Updated language specific to the EUA exception for the gammaCore Sapphire CV. Added references 34, 54, and 82.
07/01/2023	Document updated with literature review. Coverage unchanged. Added/updated the following references: 1, 3, 49, 51, 52, 54, 72, and 95.
04/15/2022	Reviewed. No changes.
05/15/2021	Document updated with literature review. Coverage unchanged. References added: 38, 41-42, 50, 54-55, 57, 60, 62-68, 70-72, 77-78, 81, 83-84, 86-89.
12/15/2020	Document updated with literature review. The following was added to Coverage: EXCEPTION: The gammaCore Sapphire CV has been issued emergency use authorization (EUA) by the U.S. Food and Drug Administration (FDA) for acute use at home or in a healthcare setting to treat adult patients with known or suspected COVID-19 who are experiencing exacerbation of asthma-related dyspnea and reduced airflow, and for whom approved drug therapies are not tolerated or provide insufficient symptom relief as assessed by their healthcare provider. Per the FDA EUA, the gammaCore Sapphire CV is not intended for use in patients with: an active implantable medical device, such as a pacemaker, hearing aid implant or any implanted electronic device; OR, a metallic device, such as a stent, bone plate, or bone screw, implanted at or near the neck; OR, an open wound, rash, infection, swelling, cut, sore, drug patch, or surgical scar(s) on their neck at the treatment location. Reference 93 added.
08/15/2020	Reviewed. No changes.
06/15/2019	Document updated with literature review. The following Coverage for Vagus Nerve Stimulation had statements edited, the intent of the Coverage

	statements are unchanged. 1) Removed the word “Implantable” from the first two coverage statements, 2) Added the word “Transcutaneous” to the nonimplantable statement. 3) Added the condition “upper-limb impairment due to stroke” and removed “obesity” from the experimental investigational and /or unproven statement. Coverage statements for Vagus Nerve Blocking Therapy for Treatment of Obesity have been removed from this document and are now housed on medical policy SUR701.039. Title changed from: Vagus Nerve Stimulation (VNS) and Vagal Nerve Blocking Therapy. References added are: 1-3, 5-21, 23, 25-26, 28, 33, 66-68, 77, 81, and 85-93. Some references were removed.
08/01/2017	Reviewed. No changes.
11/01/2016	Document updated with literature review. The following change was made to coverage: Intra-abdominal and in all situations, including but not limited to was added to the following statement: Intra-abdominal vagal nerve blocking therapy is considered experimental, investigational and/or unproven in all situations, including but not limited to the treatment of obesity. Title changed from Vagus Nerve Stimulation (VNS).
07/01/2015	Reviewed. No changes.
10/15/2014	Document updated with literature review. Coverage changed to include the addition of tinnitus and traumatic brain injury to the list of experimental, investigational and /or unproven conditions. The following statement was added: Non implantable vagus nerve stimulation devices are considered experimental, investigational and/or unproven for all indications. CPT/HCPCS code(s) updated.
10/15/2013	Document updated with literature review. The following examples were added to the list of experimental, investigational and unproven conditions: heart failure, fibromyalgia. CPT/HCPCS code(s) updated.
01/01/2013	Document updated with literature review. The following was added under coverage: “Vagus nerve blocking therapy is considered experimental, investigational and unproven as a treatment for obesity.” CPT/HCPCS code(s) updated.
06/01/2011	Document updated without literature review. Coverage unchanged. CPT/HCPCS code(s) updated.
08/15/2010	Document updated with literature review. Coverage unchanged. Document name changed to Vagus Nerve Stimulation (VNS).
10/15/2008	Revised/updated entire document
12/15/2006	Revised/updated entire document
08/15/2003	Revised/updated entire document
04/01/1999	New medical document