Vagus Nerve Stimulation
Clinical Coverage Criteria

Overview

A vagus nerve stimulator consists of an implantable pulse generator and electrical lead, and an external programming system used to change the device settings. The pulse generator is surgically implanted in the left chest. The lead (wire) is then connected to the pulse generator and the left vagus nerve. Electrical signals are transmitted from the pulse generator to the vagus nerve via the lead. The external programming system is

The Food and Drug Administration (FDA) approved the VNS Therapy System (LivaNova USA., Inc., formerly Cyberonics), on July 16, 1997, for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial onset seizures, which are refractory to antiepileptic medications (PMA 970003). On July 24, 2017, the indication for refractory partial onset seizures was expanded to include children 4 years of age and older (PMA P97003 S207). This device is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients 4 years of age and older with partial onset seizures that are refractory to antiepileptic medications

On July 18, 2005, the FDA approved the VNS Therapy System (LivaNova USA., Inc., formerly Cyberonics) for the adjunctive long-term treatment of chronic or recurrent depression in patients 18 years of age or older who are experiencing a major depressive episode and have not had adequate response to four or more adequate antidepressant treatments (PMA P97003 S50).

Policy

This Policy applies to the following Fallon Health products:

☒ Fallon Medicare Plus, Fallon Medicare Plus Central (Medicare Advantage)
☒ MassHealth ACO
☒ NaviCare HMO SNP (Dual Eligible Medicare Advantage and MassHealth)
☒ NaviCare SCO (MassHealth-only)
☒ PACE (Summit Eldercare PACE, Fallon Health Weinberg PACE)
☒ Community Care (Commercial/Exchange)

Prior authorization is required for vagus nerve stimulation.

Fallon Health Clinical Coverage Criteria

Fallon Health Clinical Coverage Criteria for vagus nerve stimulation apply to Community Care and MassHealth ACO members. For Medicare members, follow coverage criteria described in the Medicare Variation section below.

These coverage criteria apply only to vagus nerve stimulation using an FDA-approved implantable vagus nerve stimulator.

Effective for dates of service on or after August 1, 2024, Fallon Health will use InterQual® Criteria when making medical necessity determinations for implantable vagus nerve stimulation.

For coverage criteria, refer to the InterQual criteria in effect on the date of service:

- InterQual® CP:Procedures, Vagus Nerve Stimulation

- InterQual® CP:Procedures, Vagus Nerve Stimulation (Pediatric)

Fallon Health makes InterQual criteria available to the public through the transparency tool on our website, effective January 1, 2024.

Revision or replacement of a cranial neurostimulator pulse generator, receiver and/or electrode array is considered medically necessary when:
1. The member continues to meet medical necessity criteria for vagus nerve stimulation; and
2. The current implanted device is no longer functioning appropriately.

Medicare Variation

Medicare statutes and regulations do not have coverage criteria for vagus nerve stimulation. Medicare has an NCD for Vagus Nerve Stimulation (160.18), Version Number 3, Effective Date of this Version 02/15/2019. National Government Services, Inc. is the Part A and B Medicare Administrative Contractor (MAC) with jurisdiction in the Plan's service area. National Government Services, Inc. does not have an LCD for vagus nerve stimulation (Medicare Coverage Database search 07/21/2025).

Medically Refractory Partial Onset Seizures
Coverage criteria for implantable VNS for patients with medically refractory partial onset seizures and are fully established by Medicare; therefore, the Plan's coverage criteria are not applicable. VNS is not reasonable and necessary for all other types of seizure disorders which are medically refractory and for whom surgery is not recommended or for whom surgery has failed (see Section C. Nationally Non-Covered Indications).

Depression
Coverage criteria for implantable VNS for patients with treatment resistant depression (TRD) are fully established by Medicare. Medicare only allows coverage of VNS for TRD through the coverage with evidence development (CED) provision when provided in a CMS-approved trial (see Section B, Nationally Covered Indications). VNS for TRD furnished outside of a Medicare-approved CED study is Nationally Non-Covered (see Section C). VNS for the treatment of depression is Nationally Non-Covered (see Section C.).

For Medicare-approved CED studies for VNS for the treatment of TRD, see CMS Coverage with Evidence Development website: https://www.cms.gov/medicare/coverage/evidence.)

All Other Uses of VNS
Medicare coverage guidance is not available for implantable VNS for indications not specifically listed as Covered or Non-Covered, nor does Medicare coverage guidance address non-invasive devices.

For implantable VNS when used as a treatment for indications not specifically listed as Covered or Non-Covered and for non-invasive VNS, the Plan's medical policy is applicable.

Link: NCD Vagus Nerve Stimulation (160.18), Version Number 3, Effective Date of this Version 02/15/2019

According to the Medicare Benefit Policy Manual, Chapter 14, while approval by the U.S. Food and Drug Administration (FDA) does not automatically guarantee coverage under Medicare, in order to be considered for coverage under Medicare, devices must be either FDA- or Institutional Review Board (IRB)-approved.

Regarding VNS for TRD, Fallon Health covers *routine costs* incurred by members participating in CMS-approved Coverage with Evidence Development (CED) studies for VNS for TRD in accordance with § 422.101(b)(1), §422.109 and MMCM, Chapter 4, Section 10.7.3 – Payment for Clinical Studies Approved under Coverage with Evidence Development (CED).

Routine costs include all items and services that are otherwise available to Medicare beneficiaries (i.e., there exists a benefit category, it is not statutorily excluded, and there is not a national noncoverage decision) and that would be otherwise furnished even if the member were not enrolled in a clinical trial.

For Billing/coding guidelines for clinical trial-related services, please refer to Fallon Health Clinical Trials Payment Policy.

MassHealth Variation

MassHealth does not have Guidelines for Medical Necessity Determination for vagus nerve stimulation (MassHealth website search 07/21/2025), therefore, the Plan's coverage criteria are applicable.

Exclusions

- Implantable vagus nerve stimulation is considered experimental/investigational and not medically necessary when coverage criteria described herein are not met. Implantable vagus nerve stimulation is considered experimental/investigational and not medically necessary as a treatment for all other conditions, including but not limited to depression, stroke, essential tremor, headaches, fibromyalgia and traumatic brain injury.
- Non- invasive (transcutaneous) vagus nerve stimulation devices (E0735) are considered experimental/investigational and not medically necessary for all indications.
- Rechargeable vagal blocking systems for all indications, including but not limited to weight reduction. (Category III CPT codes 0312T, 0313T, 0314T, 0315T, 0316T, 0317T were sunset effective January 1, 2023).
- Integrated vagus nerve neurostimulation systems (CPT 0908T-0912T) are considered experimental/investigational and not medically necessary for all indications.

Evidence Summary

Noninvasive (Transcutaneous) Vagus Nerve Stimulation

Until recently, all VNS systems required surgical implantation. Devices that allow for noninvasive stimulation of the vagus nerve have been developed, thereby forgoing the need for surgery. This is known as noninvasive vagus nerve stimulation or transcutaneous vagus nerve stimulation.

gammaCore Non-invasive Vagus Nerve Stimulator (electroCore, LLC) received De Novo approval from the FDA on October 15, 2015, for the acute treatment of pain associated with episodic cluster headache in adult patients. Subsequently, this device received FDA 510(K) clearance under Product Code PKR (subsequent Product Code QAK) for the acute treatment of pain associated with episodic cluster headache in adult patients (K171306; Product Code: PKR) on May 30, 2017. This device has received 7 additional 510(k) clearances, most recently on September 10, 2021 (K211856 Product Code PKR, QAK), and is currently marketed under the tradename gammaCore Sapphire (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm).

gammaCore Sapphire (elecrtroCore, LLC) is indicated for:

- The preventive treatment of migraine headache in adolescent (age 12 and older) and adult patients.
- The acute treatment of pain associated with migraine headache in adolescent (age 12 and older) and adult patients.
- 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.
- Treatment of hemicrania continua in adults.
- Treatment of paroxysmal hemicrania in adults.

Cluster headache (CH) is a primary headache disorder characterized by recurrent attacks of very severe unilateral headache accompanied by restlessness and cranial autonomic symptoms. CH is classified as

either episodic (eCH), with attack periods lasting between 1 week and 1 year, and separated by ≥1 month, or chronic (cCH), with attack periods of ≥1 year without remission or with remission lasting <1 month. Widely regarded as one of the most painful medical conditions, CH can also profoundly disturb quality of life by limiting patients' functionality in work-related, domestic, and social activities (Goadsby et al., 2017).

Evidence for the use of gammaCore in the treatment of cluster headache comes from 3 randomized controlled trials (Silberstein et al., 2016, Goadsby et al., 2018, and Gaul et al., 2016) and 3 non-comparative cohort studies (Nesbitt et al. 2015, Marin et al. 2018, and Trimboli et al. 2018).

ACT1

Results for ACT1 were published by Silberstein et al., 2016.
In ACT1 (ClinicalTrials.gov identifier: NCT01792817), subjects were randomized 1:1 to receive non-invasive vagus nerve stimulation (nVNS) using the gammaCore device (ElectroCore, LLC) or sham treatment for ≤1 month during a double-blind phase; completers could enter a 3-month nVNS open-label phase. The study was conducted from February 2013 to October 2014 across 20 U.S. centers, including university-based/academic medical centers and headache/pain/neurological clinics and institutes. The study was funded by electroCore, LLC.

The primary end point was response rate, defined as the proportion of subjects who achieved pain relief (pain intensity of 0 or 1) at 15 minutes after treatment initiation for the first CH attack without rescue medication use through 60 minutes. Secondary end points included the sustained response rate (15-60 minutes). Subanalyses of episodic cluster headache (eCH) and chronic cluster headache (cCH) cohorts were prespecified. Subjects self-treated up to five CH attacks in the double-blind phase; only one attack could be treated during a 12-hour period. There were no limitations on the number of attacks that could be treated in the open-label phase. As-needed use of abortive or pain-relieving rescue medications was permitted as soon as 15 minutes after initiation of each nVNS treatment.

The ACT1 study enrolled a total of 150 patients with Cluster Headache. 101 of the patients had eCH and 49 had cCH. 150 subjects were randomized with 73 randomized to the treatment group and 77 randomized to the sham group. The intent-to-treat population comprised 133 subjects: 60 nVNS-treated (eCH, n = 38; cCH, n = 22) and 73 sham-treated (eCH, n = 47; cCH, n = 26). A modified intent to treat (mITT) group was defined as all randomized subjects who treated at least one CH attack. This included 60 subjects in the treatment arm and 73 in the sham arm.

The response for the primary end point in the mITT population was 26.7% in the nVNS group and 15.1% in the sham group, which was not statistically significant but showed a trend (P=0.1). In subgroup analyses, a higher response rate was demonstrated with nVNS (34.2%) than with sham treatment (10.6%) for the eCH cohort (P=0.008) but not for the cCH cohort (nVNS, 13.6%; sham, 23.1%; P=0.48).

Sustained treatment response rates (defined as the proportion of subjects with mild or no pain without the use of rescue medication through 60 minutes after treatment initiation for the first CH attack) for the total and eCH cohort population were higher with nVNS than with sham treatment (total: nVNS, 26.7%; sham, 12.3%; eCH: nVNS, 34.2%; sham, 10.6%;). For the cCH cohort, sustained response rates were similar between groups (nVNS, 13.6%; sham, 15.4%). The proportion of subjects in the eCH cohort and total population, but not in the cCH cohort, who were responders (mild or no pain) at 15 minutes for ≥50% of the total number of treated attacks was higher with nVNS than with sham treatment (total: nVNS, 26.7%; sham, 20.6%; P=0.41; eCH: nVNS, 34.2%; sham, 14.9%; P=0.04; cCH: nVNS, 13.6%; sham, 30.8%; P=0.19). This result was statistically significant in the eCH cohort. Similarly, for those cases where data are available differences between groups favored nVNS for the change in duration of the first attack relative to the last attack before treatment in the double-blind phase and were significant in the total population (–9.5 minutes; P=0.03) and eCH cohort (–14.4 minutes; P=0.03) but not in the cCH cohort (1.0 minutes; P=0.69).

During the three-month open label period of the study the efficacy of nVNS in patients with episodic cluster headache (n=85) was consistent with the benefits observed in the double-blind phase. Compared with a response of 26.7% in the blinded phase, the response in the open label phase was 30% for the subjects who had been in the treatment arm and increased from 15.1% to 32.9% for subjects who had been in the sham arm.

In the blind and open phases of the ACT1 study there were 1772 headaches treated over a period of four months. The greatest number of treatments to any subject was 112. There were no device related serious adverse events in the in this study. The majority of the adverse events were mild and transient and occurred during the time of active treatment.

ACT2

Results of ACT2 were published by Goadsby et al., 2017.
ACT2 (ClinicalTrials.gov identifier: NCT01958125) was a randomized, double-blind sham controlled post-market study conducted in four European countries at nine tertiary care sites, including academic medical centers and headache/pain/neurology clinics. The study was conducted between September 10, 2013, and October 14, 2014, and consisted of 3 phases. The first phase of the study was a 1-week run-in period, during which subjects continued to use their standard of care treatments for acutely treating their cluster headaches and recorded the duration, frequency and the use of medication for each attack. During the second phase of the study, subjects were randomized to treatment with either an active gammaCore or sham device and remained blinded to the randomization assignment for the duration of the 2-week phase. The third phase was open label during which all subjects treated their cluster headache attacks with an active gammaCore device for an additional 2 weeks, according to the same instructions for use followed during the second phase. The study was funded by electroCore, LLC.

All efficacy endpoints were assessed for the total cohort and the eCH and cCH subgroups. The primary efficacy endpoint was the proportion of all treated attacks that achieved pain-free status (i.e. pain score of 0) within 15 minutes after treatment initiation. Secondary efficacy endpoints included the mean proportion of treated attacks per subject that achieved responder status (i.e. pain score of 0 or 1) within 30 minutes, mean proportion of treated attacks per subject that achieved pain-free status within 30 minutes, and mean change in pain intensity from attack onset to 15 and 30 minutes after treatment initiation. The proportions of subjects who achieved pain-free status and who achieved responder status in ≥50% of treated attacks at 15 minutes were evaluated as exploratory efficacy end points to allow parallel comparison with results from other studies.

Each subject enrolled in the study was instructed to treat all cluster headache attacks that are at least six hours apart, as soon as possible after onset over a total period of two weeks. If an attack was not treated with the device, the subject still recorded the attack and the medication/treatment for the attack. Each self-administered treatment consisted of three 120-second stimulation cycles applied consecutively at the onset of the attack. If the attack was not aborted the subject could stimulate with an additional three consecutive 120 second cycles at nine minutes. If the attack was not aborted within 15 minutes from the start of the device treatment, the subject could use their standard of care treatment (medication and/or oxygen). Patients were required to wait at least 6 hours following the treatment of a cluster attack before treating a second attack. If a cluster headache attack was not treated with the gammaCore (within the 6-hour period, or otherwise) the subject still recorded the attack, and the medication/treatment used for the attack.

In the ACT2 study subjects were asked to refrain from starting new prophylactic treatment or changing the dose of any medication for cluster headache once the run-in period started and agreed to maintain their existing cluster headache treatment regimens during the run-in and double-blind periods. Subjects were allowed to use their usual rescue treatments (prescribed or over the counter) to relieve cluster headache attacks that were not aborted with the study device but were asked to refrain from use of rescue treatments for 15 minutes after initiation of treatment with the study device for an attack.
In the ACT2 Study, subjects were instructed to treat their cluster headache attack at the onset of pain with three 2-minute stimulations, with stimulation to the neck ipsilateral to the side of the head where the

cluster headache originated. If pain was still present at nine minutes the subjects had the option of treating with an additional three 2-minute stimulations.

The ACT2 Study enrolled a total of 102 patients with CH (eCH n = 30; cCh n = 72).

The primary outcome for effectiveness defined in the ACT2 study was the percentage of total attacks that were pain-free at 15 minutes after initiation of treatment with the device with no use of rescue medication through the treatment period (30 minutes).

The results for the primary end point in the total population were 13.5% in the nVNS group and 11.5% in the sham group and the difference between the two was not statistically significant (P=0.713). In the eCH cohort, a higher percentage of attacks were pain free with nVNS than with sham treatment (nVNS 47.5%; sham 6.2%; P<0.01) but not for the cCH cohort where the sham group performed better (nVNS, 4.8%; sham, 12.9%; P=0.13).

The proportion of each patient's attacks that responded (pain score of 0 or 1 and no rescue medication) 30 minutes after the initiation of gammaCore treatment was higher than the sham results in the both the chronic and episodic CH groups. (total: nVNS, 43%; sham, 28%; eCH: nVNS, 58%; sham, 25%; cCH: 37%; sham 28%). In patients with eCH there was a reduction in their reported average pain intensity 15 minutes after treatment on a five-point scale (nVNS, – 1.7; sham, –0.6;) and a lessor change in the total population of the cCH cohort (total: nVNS, – 1.3; sham, –0.9; cCH: nVNS, –1.2; sham, –1.0). The percentage of patients who reported mild or no pain 30 minutes after treatment initiation for ≥50% of their attacks was higher for the cCH and eCH groups (total: nVNS, 39.6%; sham, 13.6%; eCH: nVNS, 64.3%; sham, 15.4%; cCH: nVNS, 29.4%; sham, 12.9%). The proportion of subjects with ≥1 ADE was similar between the nVNS (18%) and sham (19%) groups during the double-blind period and was 12% during the open-label period.

In the ACT2 study there were 1326 headaches treated in 102 subjects over a 4-week period in the blind and open parts of the study. The greatest number of treatments in any individual was 59. There were no device related serious adverse events. The majority of the adverse events were mild and transient and occurred during the time of active treatment.

The FDA conducted a posthoc analysis of ACT1 and ACT2 studies to further examine the therapeutic benefit of gammaCore for the acute treatment of episodic cluster headache. The data from each study was analyzed using as close an approximation as was possible to the other study's end point. Because ACT1 defined the use of rescue medication within sixty minutes to be a treatment failure while ACT2 defined use of rescue medication within thirty minutes as a treatment failure and considering other differences in the way the treatment was delivered in ACT1 and ACT2, the comparison is not exact. For the ACT1 primary endpoint the result was statistically significant for the eCH subgroup. The pattern in the ACT2 data are consistent with this result. Taken in total, these two studies support a clinically meaningful benefit in a portion of the episodic cluster headache population. Patients for whom this device is effective might be expected to feel relatively immediate relief from the intense pain of a cluster headache while individuals for whom it is not effective will rapidly seek other forms of relief (FDA De Novo Summary DEN150048).

PREVA

Results of PREVA were published by Gaul et al., 2016.
The PREVention and Acute treatment of chronic cluster headache (PREVA) study of non-invasive vagus nerve stimulation (nVNS) (gammaCore) was a Phase III, open label, randomized controlled trial. Participants were aged 18 to 70 years and were diagnosed with chronic CH according to *International Classification of Headache Disorders* criteria ≥1 year before enrollment. The study was conducted from October 2012 through March 2014, involved 10 European sites: five in Germany, three in the United Kingdom, one in Belgium, and one in Italy. The study was funded by electroCore, LLC. After a 2-week baseline phase, in which all participants received their individualized standard of care (SoC) therapy, patients were randomly assigned (1:1) to receive nVNS + SoC or SoC alone during a 4-week randomised

phase. An optional 4-week extension phase followed, with all patients receiving nVNS + SoC. The nVNS-treated patients self-administered three 2-minute prophylactic stimulations (each separated by a period of 5 min) to the right side of the neck (right vagus nerve); this preventive treatment regimen occurred twice daily for a total of 6 stimulations per day. Three additional nVNS stimulations were permitted as needed for the acute treatment of individual CH attacks. Patients were permitted to receive abortive medications if their CH attacks persisted beyond 15 min after stimulation.

The primary end point was the reduction in the mean number of CH attacks per week, defined as the number of attacks during the last two weeks of the randomised phase minus the number of attacks during baseline divided by 2. Attack frequency was evaluated during the last two weeks of the four-week randomised phase to ensure sufficient time for nVNS to demonstrate its full effect. Reductions in the mean number of CH attacks per week were also evaluated during the last two weeks of the extension phase. Secondary efficacy end points included ≥50% response rate (i.e. proportion of participants with ≥50% reduction in mean number of CH attacks per week), abortive medication use and duration and intensity of CH attacks that were acutely treated with nVNS. Participant-completed headache diaries captured the number of CH attacks, CH pain intensity (five-point scale: none to very severe), CH duration and abortive medication use.

Of the 114 individuals enrolled and assessed at baseline, 97 were randomly assigned to treatment and constituted the safety population (SoC plus nVNS, n = 48; control, n = 49); 92 continued into the extension phase (SoC plus nVNS, n = 44; control, n = 48); and 70 completed the study (SoC plus nVNS, n = 33; control, n = 37). Of the 97 individuals in the safety population, 93 met the criteria for inclusion in the ITT population (SoC plus nVNS, $n = 45$; control, $n = 48$).

In the ITT population, participants receiving SoC plus nVNS during the randomised phase had a greater reduction from baseline (−5.9; SE, 1.2) in the number of CH attacks per week than those receiving control (−2.1; SE, 1.2), for a mean therapeutic gain of 3.9 fewer CH attacks per week (95% confidence interval (CI): 0.5, 7.2; p = 0.02).

Among participants in the ITT population, a significantly higher ≥ 50% response rate during the randomised phase was observed in the SoC plus nVNS group (40% (18/45)) than in the control group (8.3% (4/48)) ($p < 0.001$). No serious treatment-related adverse events occurred.

During the randomised phase, 93.8% (45/48) of individuals assigned to SoC plus nVNS acutely treated ≥1 CH attack with nVNS; during the extension phase, 68.2% (30/44) and 83.3% (40/48) assigned to SoC plus nVNS and control, respectively, acutely treated ≥1 CH attack with nVNS.

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). 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 published a Medtech innovation briefing on noninvasive VNS for cluster headache (MIB162). 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. 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). 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."

Integrated Vagus Nerve Neurostimulation Systems

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that causes persistent synovitis, bone damage, and progressive joint destruction. Neuroimmune modulation through electrical stimulation of the vagus nerve activates the inflammatory reflex and has been shown to inhibit the production and release of inflammatory cytokines and decrease clinical signs and symptoms in RA.

A novel neuroimmune modulation system (SetPoint Medical, Valencia, CA) explicitly designed to activate the inflammatory reflex for the treatment of RA was developed and tested in a first-in-human clinical study (Genovese et al. 2020). Results indicated that the device was safe and well tolerated. Furthermore, the treatment led 50% of patients with multiple drug-refractory RA to achieve clinically meaningful responses in disease activity and reductions in inflammatory cytokines. Based on these findings, the RESET-RA study (ClinicalTrials.gov ID NCT04539964) was designed to further evaluate this approach and device in a larger sham-controlled study.

The RESET-RA study is a randomized, double-blind, sham-controlled, multicenter, two-stage pivotal trial that enrolled adult patients with active, moderate to severe RA who were incomplete responders or intolerant to at least one biologic or targeted synthetic disease-modifying anti-rheumatic drug (DMARD). The efficacy primary endpoint is after 12 weeks of stimulation, and patients will then be followed across a long-term extension period (180 weeks). RESET-RA is funded by SetPoint Medical.

Stage 1, comprising the first 60 patients enrolled, was initiated in January 2021 (first patient implanted) and completed enrollment in March 2022. A preplanned interim analysis of Stage 1 was conducted to check for safety risks and a lack of efficacy before enrolling patients in Stage 2. Additionally, a stopping rule, predefined as a difference of less than 10% between the treatment and sham groups in the proportion of American College of Rheumatology 20 (ACR20) responders at the Week 12 primary endpoint, was established to prevent the continuation of a trial with a projected low probability of success. The stopping rule was not met, and the US Food and Drug Administration approved the initiation of Stage 2 of the study in July 2022.

The SetPoint System consists of 2 implanted components: a miniaturized pulse generator with integrated electrodes and a silicon pod that positions the pulse generator on the left vagus nerve; and two external components: the wireless charger and an iPad application for programming the pulse generator. The pulse generator is implanted on the left cervical vagus nerve within the carotid sheath. The silicon pod holds the pulse generator in close apposition to the nerve and electrically insulates the device from surrounding tissues. Once implanted, the vagus nerve fits into a groove on the base of the pulse generator, where the electrodes are oriented in direct apposition to the nerve for efficient stimulation. The device is powered by a rechargeable lithium-ion battery with a usage life of at least 10 years. The pulse generator is recharged using a proprietary radio frequency-based external wireless charger worn around the neck for a few minutes weekly. The charger also provides wireless telemetry for the transmission and receipt of information with an Apple® iPad-based software application, which healthcare professionals use to program and monitor implants.

All eligible subjects will undergo the surgery under general anesthesia. Half of the subjects will receive active stimulation (the treatment group), and the other half will receive non-active stimulation (the control group). Stimulation will be delivered for 1 minute once per day for 12 weeks. After completing primary endpoint assessments at Week 12, there will be a one-way crossover of control subjects to active stimulation and a 252-week open-label follow-up with all subjects (treatment and control) receiving active stimulation to evaluate long-term safety. Blinding will be maintained until the last enrolled and randomized subject in Stage 2 completes Week 12 assessments, and the study database is locked.

A predefined blinded interim analysis was performed in patients enrolled in the study's initial stage (Stage 1) that included demographics, enrollment rates, device implantation rates, and safety of the surgical procedure, device, and stimulation over 12 weeks of treatment, and results are reported by Peterson et al., 2024.

All device implant procedures were completed without intraoperative complications, infections, or surgical revisions. No unanticipated adverse events were reported during the perioperative period and at the end of 12 weeks of follow-up. No study discontinuations were due to adverse events, and no serious adverse events were related to the device or stimulation. Two serious adverse events were related to the implantation procedure: vocal cord paresis and prolonged hoarseness. These were reported in two patients and are known complications of surgical implantation procedures with vagus nerve stimulation devices. The adverse event of vocal cord paresis resolved after vocal cord augmentation injections with filler and speech therapy. The prolonged hoarseness had improved with speech therapy, but mild hoarseness persists (Peterson et al., 2014).

The Primary Completion Date for RESET-RA was May 16, 2025. Clinical efficacy and patient-reported effectiveness outcomes will be presented in a forthcoming report.

SetPoint Medical received FDA Premarket Approval (PMA) on August 6, 2025, for the SetPoint System, a novel neuroimmune modulation device (P240039). The SetPoint System is indicated for adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response, loss of response, or intolerance to one or more biological or targeted synthetic disease modifying antirheumatic drugs (b/tsDMARDs).

Published evidence for the SetPoint System is limited to results of a first in-human pilot study (ClinicalTrials.gov ID NCT03437473). Participants with moderately to severely active rheumatoid arthritis and prior insufficient response to two or more biological disease-modifying anti-rheumatic drugs or Janus kinase inhibitors with at least two different modes of action were enrolled in a two-stage study done at five clinical research sites in the USA. Stage 1 was open label; participants were implanted with a miniaturized VNS device, which was activated for 1 min once a day. In stage 2, participants were randomly assigned (1:1:1) to receive active stimulation (1 min once a day or 1 min four times a day) or sham stimulation (device implanted but not activated), with the sites and participants masked to treatment assignment. The primary outcome was incidence of treatment-emergent adverse events. Clinical efficacy was assessed as a key secondary outcome. Fourteen patients were enrolled between March 13 and Aug 8, 2018. Three patients received stimulation in stage 1 and, following safety review board approval, the remaining 11 patients were implanted during stage 2 and randomly assigned to receive 1 min of stimulation once daily (n=3), 1 min of stimulation four times daily (n=4), or no stimulation (n=4) for 12 weeks. There were no device-related or treatment-related serious adverse events. Surgery-related adverse events were Horner's syndrome and vocal cord paralysis (in one patient each), which resolved without clinically significant sequelae. No deaths were recorded (Genovese et al., 2020).

On October 2, 2024, SetPoint Medical announced it had received Investigational Device Exemption (IDE) approval from the U.S. Food and Drug Administration (FDA) to study its proprietary neuroimmune modulation platform in people living with relapsing-remitting multiple sclerosis (RRMS). The multicenter,

randomized, double-blind, sham-controlled pilot study will be initiated in 2025 and will enroll up to 60 patients across the United States.[1]

Analysis of Evidence (Rationale for Determination)

Non-Invasive (Transcutaneous) Vagus Nerve Stimulation
Evidence for the use of the gammaCore device for non-invasive vagus nerve stimulation (nVNS) in the treatment of cluster headache comes from 3 randomized controlled trials and 3 non-comparative cohort studies. In these studies, non-invasive vagus nerve stimulation appears to be effective in some but not all people with episodic CH.

PREVA examined the clinical benefit of prophylactic nVNS therapy in a treatment-refractory chronic CH population. This study met its primary end point by demonstrating that daily adjunctive prophylactic nVNS therapy significantly reduced the number of CH attacks per week. Study limitations include the lack of a placebo/sham device, an open-label study design, the short treatment duration (< 1 month) and the use of patient-reported outcomes.

Two RCTs have evaluated nVNS for treatment of acute cluster headache compared to sham nVNS. Treatment periods ranged from 2 weeks to 1 month. 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. In the ACT2 study, nVNS was superior to sham therapy for acute treatment of attacks in patients with eCH but not those with cCH or in the total population. Primary end point results were significant for the eCH cohort but were diminished overall by the cCH cohort results. These results confirm and extend findings from the previous ACT1 study and demonstrate that nVNS is an effective acute attack treatment option for patients with eCH, with a favorable risk/benefit profile. ACT1 and ACT2 had limitations, including short duration, which did not allow for evaluation of response with long-term nVNS therapy.

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.

Integrated Vagus Nerve Neurostimulation Systems
The SetPoint System (SetPoint Medical) received FDA PMA approval on August 6, 2025 (P240039). The SetPoint System is indicated for adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response, loss of response, or intolerance to one or more biological or targeted synthetic disease modifying antirheumatic drugs (b/tsDMARDs). FDA approval for the SetPoint System was based on the results of the RESET-RA study. The Primary Completion Date for RESET-RA was May 16, 2025. Clinical efficacy and patient-reported effectiveness outcomes from RESET-RA are forthcoming. At this time, published evidence for efficacy of the SetPoint System is not available.

Coding

The following codes are included below for informational purposes only; inclusion of a code does not constitute or imply coverage.

Do not report CPT 64568 in conjunction with CPT 61885, 61886, or 64570).

Do not report CPT 61888 in conjunction with CPT 61885 or 61886 for the same pulse generator.

Do not report CPT 64570 in conjunction with CPT 61888.

[1] SetPoint Medical Receives FDA's IDE Approval for U.S. Pilot Study of Neuroimmune Modulation Platform in Adults with Relapsing-Remitting Multiple Sclerosis
https://setpointmedical.com/fda-ide-approval-us-pilot-study-neuroimmune-modulation-platform-multiple-sclerosis/

Code	Description
Full system placement or replacement	
64568	Open Implantation of cranial nerve (eg, vagus nerve) neurostimulator electrode array and pulse generator
Generator/battery replacement	
61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
61886	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to 2 or more electrode arrays
64569	Revision or replacement of cranial nerve (eg, vagus nerve) neurostimulator electrode array, including connection to existing pulse generator
64570	Removal of cranial nerve (eg, vagus nerve) neurostimulator electrode array and pulse generator
Removal of generator	
61888	Revision or removal of cranial neurostimulator pulse generator or receiver
Analysis and programming	
95970	Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve, neurostimulator pulse generator/transmitter, without programming
95976	Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with simple cranial nerve neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional
95977	Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with complex cranial nerve neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional

Device C-codes

Code	Description
C1767	Generator, neurostimulator (implantable), non-rechargeable
C1778	Lead, neurostimulator (implantable)

Device L-codes

Code	Description
L8680	Implantable neurostimulator electrode, each
L8686	Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension

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Policy history

Origination date:	01/01/2014
Review/Approval(s):	Technology Assessment Committee 10/23/2013 (Adopted InterQual Criteria) 01/28/2015 (annual review) 01/27/2016 (annual review), 01/25/2017 (annual review), 01/24/2018 (annual review), 01/23/2019 (annual review); 05/27/2020 (adopted Fallon Health criteria), 02/08/2022 (Added clarifying language related to Medicare Advantage, NaviCare and PACE under policy section), 07/23/2024 (annual review, adopted InterQual Criteria), 07/22/2025 (annual review, updated Evidence Summary and Analysis of Evidence to include Noninvasive (Transcutaneous) Vagus Nerve Stimulation and Integrated Vagus Nerve Neurostimulation Systems, no changes to coverage criteria, added Exclusion for Integrated vagus nerve neurostimulation systems (CPT 0908T-0912T), updated References). Utilization Management Committee: 08/19/2025 (annual review, approved with no changes to coverage criteria).

Instructions for Use

Fallon Health complies with CMS's national coverage determinations (NCDs), local coverage determinations (LCDs) of Medicare Contractors with jurisdiction for claims in the Plan's service area, and applicable Medicare statutes and regulations when making medical necessity determinations for Medicare Advantage members. When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, Fallon Health may create internal coverage criteria under specific circumstances described at § 422.101(b)(6)(i) and (ii).

Fallon Health generally follows Medical Necessity Guidelines published by MassHealth when making medical necessity determinations for MassHealth members. In the absence of Medical Necessity Guidelines published by MassHealth, Fallon Health may create clinical coverage criteria in accordance with the definition of Medical Necessity in 130 CMR 450.204.

For plan members enrolled in NaviCare, Fallon Health first follows CMS's national coverage determinations (NCDs), local coverage determinations (LCDs) of Medicare Contractors with jurisdiction for claims in the Plan's service area, and applicable Medicare statutes and regulations when making medical necessity determinations. When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, or if the NaviCare member does not meet coverage criteria in applicable Medicare statutes, regulations, NCDs or LCDs, Fallon Health then follows Medical Necessity Guidelines published by MassHealth when making necessity determinations for NaviCare members.

Each PACE plan member is assigned to an Interdisciplinary Team. PACE provides participants with all the care and services covered by Medicare and Medicaid, as authorized by the interdisciplinary team, as well as additional medically necessary care and services not covered by Medicare and Medicaid. With the exception of emergency care and out-of-area urgently needed care, all care and services provided to PACE plan members must be authorized by the interdisciplinary team.

Not all services mentioned in this policy are covered for all products or employer groups. Coverage is based upon the terms of a member's particular benefit plan which may contain its own specific provisions for coverage and exclusions regardless of medical necessity. Please consult the product's Evidence of Coverage for exclusions or other benefit limitations applicable to this service or supply. If there is any discrepancy between this policy and a member's benefit plan, the provisions of the benefit plan will govern. However, applicable state mandates take precedence with respect to fully insured plans and self-

funded non-ERISA (e.g., government, school boards, church) plans. Unless otherwise specifically excluded, federal mandates will apply to all plans