

7.01.143	Responsive Neurostimulation for the Treatment of Refractory Focal Epilepsy		
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Section:	7.0 Surgery	Page:	Page 1 of 14

Policy Statement

Responsive neurostimulation (RNS) may be considered **medically necessary** for patients with focal epilepsy who meet **all** of the following criteria:

- Are 18 years or older
- Are not candidates for focal resective epilepsy surgery (e.g., have an epileptic focus near the eloquent cerebral cortex; have bilateral temporal epilepsy)
- Are refractory to medical therapy (have failed 2 or more appropriate antiepileptic medications at therapeutic doses)
- Do not have contraindications for responsive neurostimulation device placement (see Policy Guidelines section)
- Have a diagnosis of focal seizures with 1 or 2 well-localized seizure foci identified
- Have an average of 3 or more disabling seizures (e.g., motor focal seizures, complex focal seizures, or secondary generalized seizures) per month over the prior 3 months

Responsive neurostimulation is considered **investigational** for all other indications.

Policy Guidelines

Contraindications for responsive neurostimulation device placement include 3 or more specific seizure foci, presence of primary generalized epilepsy, or presence of a rapidly progressive neurologic disorder.

Coding

There are no specific CPT codes for the insertion of this device. It would be reported with the CPT codes for insertion of a neurostimulator such as the following:

- **61850:** Twist drill or burr hole(s) for implantation of neurostimulator electrodes, cortical
- **61860:** Craniectomy or craniotomy for implantation of neurostimulator electrodes, cerebral, cortical
- **61863:** Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; first array
- **61864:** Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; each additional array (List separately in addition to primary procedure)
- **61880:** Revision or removal of intracranial neurostimulator electrodes
- **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
- **61888:** Revision or removal of cranial neurostimulator pulse generator or receiver
- **95970:** Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain, cranial

nerve, spinal cord, peripheral nerve, or sacral nerve, neurostimulator pulse generator/transmitter, without programming

- **95971:** Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with simple spinal cord or peripheral nerve (e.g., sacral nerve) neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional

Description

Responsive neurostimulation (RNS) for the treatment of epilepsy involves the use of one or more implantable electric leads that serve both a seizure detection and neurostimulation function. The device is programmed using a proprietary algorithm to recognize seizure patterns from electrocorticography output and to deliver electrical stimulation with the goal of terminating a seizure. One device, the NeuroPace RNS System, has U.S. Food and Drug Administration approval for the treatment of refractory focal (formerly partial) epilepsy.

Related Policies

- Deep Brain Stimulation
- Vagus Nerve Stimulation

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

In November 2013, the NeuroPace RNS® System (NeuroPace) was approved by the FDA through the premarket approval process for the following indication¹³:

"The RNS® System is an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures who have undergone diagnostic testing that localized no more than 2 epileptogenic foci, are refractory to two or more antiepileptic medications, and currently have frequent and disabling seizures (motor partial seizures, complex partial seizures and/ or secondarily generalized seizures). The RNS® System has demonstrated safety and effectiveness in patients who average 3 or more disabling seizures per month over the three most recent months (with no month with fewer than two seizures), and has not been evaluated in patients with less frequent seizures."

FDA product code: PFN.

Rationale

Background

Seizures and Seizure Disorders

Focal seizures (previously referred to as partial seizures) arise from a discrete area of the brain and can cause a range of symptoms, depending on the seizure type and the brain area involved.

Note that the term *focal seizure* in older literature may be referred to as “partial seizure.” A position paper from the International League Against Epilepsy (2017) outlined updated terminology for seizure and epilepsy subtypes.¹ For example, focal-onset seizures are subdivided based on the associated level of consciousness, and subsequently into whether they are motor or non-motor-onset.

Seizure disorders may be grouped into epileptic syndromes based on a number of factors, including the types of seizures that occur and their localization, the age of onset, patterns on electroencephalogram, associated clinical or neuroimaging findings, and genetic factors. Temporal lobe epilepsy is the most common syndrome associated with focal seizures. Of those with focal seizures, 30% to 40% have intractable epilepsy, defined as a failure to control seizures after 2 seizure medications have been appropriately chosen and used.²

Epilepsy Treatment

Medical Therapy for Seizures

Standard therapy for seizures, including focal seizures, includes treatment with one or more of various antiepileptic drugs (AEDs), which include newer AEDs, like oxcarbazepine, lamotrigine, topiramate, gabapentin, pregabalin, levetiracetam, tiagabine, and zonisamide.² Currently, response to AEDs is less than ideal: 1 systematic review comparing newer AEDs for refractory focal epilepsy reported an overall average responder rate in treatment groups of 34.8%.² As a result, a substantial number of patients do not achieve good seizure control with medications alone.

Surgical Therapy for Seizures

When a discrete seizure focus can be identified, seizure control may be achieved through resection of the seizure focus (epilepsy surgery). For temporal lobe epilepsy, a randomized controlled trial has demonstrated that surgery for epilepsy was superior to prolonged medical therapy in reducing seizures associated with impaired awareness and in improving quality of life.³ Surgery for refractory focal epilepsy (excluding simple focal seizures) is associated with 5-year freedom from seizure rates of 52%, with 28% of seizure-free individuals able to discontinue AEDs.⁴ Selection of appropriate patients for epilepsy surgery is important, because those with nonlesional extratemporal lobe epilepsy have worse outcomes after surgery than those with nonlesional temporal lobe epilepsy.⁵ Some patients are not candidates for epilepsy surgery if the seizure focus is located in an eloquent area of the brain or other region that cannot be removed without risk of significant neurologic deficit.

Neurostimulation for Neurologic Disorders

Electrical stimulation at one of several locations in the brain has been used as therapy for epilepsy, either as an adjunct to or as an alternative to medical or surgical therapy. Vagus nerve stimulation (VNS) has been widely used for refractory epilepsy, following Food and Drug Administration (FDA) approval of a VNS device in 1997 and 2 randomized controlled trials evaluating VNS in epilepsy.⁶ Although the mechanism of action for VNS is not fully understood, VNS is thought to reduce seizure activity through activation of vagal visceral afferents with diffuse central nervous system projections, leading to a widespread effect on neuronal excitability.

Stimulation of other locations in the neuroaxis has been studied for a variety of neurologic disorders. Electrical stimulation of deep brain nuclei (deep brain stimulation [DBS]) involves the

use of chronic, continuous stimulation of a target. It has been most widely used in the treatment of Parkinson disease and other movement disorders, and has been investigated for treating epilepsy. DBS of the anterior thalamic nuclei was studied in a randomized control trial, the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy trial, but DBS is not currently approved by the FDA for stimulation of the anterior thalamic nucleus.⁷ Stimulation of the cerebellar and hippocampal regions and the subthalamic, caudate, and centromedian nuclei have also been evaluated for the treatment of epilepsy.⁶

Responsive Neurostimulation for Epilepsy

Responsive neurostimulation (RNS) shares some features with DBS, but is differentiated by its use of direct cortical stimulation and by its use in both monitoring and stimulation. The RNS system provides stimulation in response to detection of specific epileptiform patterns, while DBS provides continuous or intermittent stimulation at preprogrammed settings.

Development of the RNS system arose from observations related to the effects of cortical electrical stimulation for seizure localization. It has been observed that electrical cortical stimulation can terminate induced and spontaneous electrographic seizure activity in humans and animals.⁸ Patients with epilepsy may undergo implantation of subdural monitoring electrodes for the purposes of seizure localization, which at times have been used for neurostimulation to identify eloquent brain regions. Epileptiform discharges that occur during stimulation for localization can be stopped by a train of neighboring brief electrical stimulations.⁹

In tandem with the recognition that cortical stimulation can stop epileptiform discharges was development of fast pre-ictal seizure prediction algorithms. These algorithms interpret electrocorticographic data from detection leads situated over the cortex. The RNS process thus includes electrocorticographic monitoring via cortical electrodes, analysis of data through a proprietary seizure detection algorithm, and delivery of electrical stimulation via both cortical and deep implanted electrodes in an attempt to halt a detected epileptiform discharge.

One device, the NeuroPace RNS System, is currently approved by the FDA and is commercially available.

RNS for Seizure Monitoring

Although the intent of the electrocorticography component of the RNS system is to provide input as a trigger for neurostimulation, it also provides continuous seizure mapping data (chronic unlimited cortical electrocorticography) that may be used by practitioners to evaluate patients' seizures. In particular, the seizure mapping data have been used for surgical planning of patients who do not experience adequate seizure reduction with RNS placement. Several studies have described the use of RNS in evaluating seizure foci for epilepsy surgery¹⁰, or for identifying whether seizure foci are unilateral.^{11,12}

This review does not further address use of RNS exclusively for seizure monitoring.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 to 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 a technology, 2 domains are examined: the relevance and the 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.

Clinical Context and Test Purpose

The purpose of responsive neurostimulation in individuals with refractory focal epilepsy is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: does responsive neurostimulation therapy improve the net health outcome in patients with refractory focal epilepsy?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is individuals with refractory focal epilepsy. Focal seizures (previously referred to as partial seizures) arise from a discrete area of the brain and can cause a range of symptoms, depending on the seizure type and the brain area involved. Focal seizures are further grouped into simple focal seizures, which may be associated with motor, sensory, or autonomic symptoms, or complex focal seizures, in which consciousness is affected. Complex focal seizures may be associated with abnormal movements (automatisms). In some cases, focal seizures may result in secondary generalization, in which widespread brain electrical activity occurs after the onset of a focal seizure, thereby resulting in a generalized seizure.

Interventions

The therapy being considered is responsive neurostimulation.

One device, the NeuroPace RNS System, is currently approved by the FDA and is commercially available. The system consists of an implantable neurostimulator, a cortical strip lead, a depth lead, a programmer and telemetry wand, and a patient data management system. Before device implantation, the patient undergoes seizure localization, which includes inpatient video-electroencephalographic monitoring and magnetic resonance imaging for detection of epileptogenic lesions. Additional testing may include electroencephalography with intracranial electrodes, intraoperative or extraoperative stimulation with subdural electrodes, additional imaging studies, and/or neuropsychological testing and intracarotid amytal (Wada) testing. The selection and location of the leads are based on the location of seizure foci. Cortical strip leads are recommended for seizure foci on the cortical surface, while the depth leads are recommended for seizure foci beneath the cortical surface. The implantable neurostimulator and cortical and/or depth leads are implanted intracranially. The neurostimulator is initially programmed in the operating room to detect electrocorticographic activity. Responsive therapy is initially set up using standard parameters from the electrodes from which electrical activity is detected. Over time, the responsive stimulation settings are adjusted on the basis of electrocorticography data, which are collected by the patient through interrogation of the device with the telemetry wand and transmitted to the data management system.¹⁴

Comparators

Because RNS is considered for patients refractory to other treatments, the appropriate comparison group could consist of other treatments for focal epilepsy considered to be efficacious, including medical management, surgical management, other types of implanted stimulators (e.g., vagal nerve stimulators), or a combination. In patients with treatment-refractory epilepsy, the disease is expected to have a natural history involving persistent seizures. Therefore, studies that compare seizure rates and seizure-free status pre- and post-RNS treatment may also provide evidence about the efficacy of the RNS device.

Outcomes

The general outcomes of interest are symptoms, morbid events, quality of life, and treatment-related mortality and morbidity.

RNS for Treatment of Refractory Focal Epilepsy

The body of evidence addressing whether RNS is associated with improved health outcomes for patients with focal epilepsy includes an industry-sponsored RCT, which was used for the device's U.S. Food and Drug Administration (FDA) approval, as well as multiple case series and case reports.

Pivotal Trial

RNS for epilepsy was evaluated in the RNS System Pivotal Trial, a multicenter, double-blinded, sham-controlled trial that served as the basis of FDA's approval of the device.¹⁵ Published by Morrell et al (2011), this RCT included 191 patients with medically intractable focal epilepsy who were implanted with the RNS device and randomized to treatment or sham control after a 1-month postimplant period during which time no subjects had the device activated. Eligible patients were adults with focal seizures whose epilepsy had not been controlled with at least 2 trials of antiepileptic drugs (AEDs), who had at least 3 disabling seizures (motor focal seizures, complex focal seizures, or secondary generalized seizures) per month on average, and who had standard diagnostic testing that localized 1 or 2 epileptogenic foci. Thirty-two percent of those implanted had prior epilepsy surgery, and 34% had a prior vagal nerve stimulator.

Patients were randomized to active stimulation (n=97) or sham stimulation (n=94). After the 4-week postoperative period, patients received either sham or active stimulation according to group assignment. There was a 4-week stimulation optimization period, followed by a 3-month blinded evaluation period. In the evaluation period, all outcome data were gathered by a physician blinded to group assignment, and the neurostimulator was managed by a nonblinded physician. One patient in each group did not complete the stimulus optimization period (one due to subject preference in the active stimulation group; one due to death in the sham stimulation group). An additional patient in each group did not complete the blinded evaluation phase due to emergent explant of the device. After the 3-month blinded evaluation period, all patients received active stimulation during an open-label follow-up period. At the time of the Morrell publication, 98 subjects had completed the open-label period and 78 had not. Eleven patients did not complete the open-label follow-up period (5 due to death, 2 to emergent explant, 4 to study withdrawal).

The trial's primary effectiveness objective was to demonstrate a significantly greater reduction in the frequency of total disabling seizures in the treatment group compared with the sham group during the blinded evaluation period relative to baseline (preimplant). The mean preimplant seizure frequency per month in the treatment group was 33.5 (range, 3-295) and 34.9 (range, 3-338) in the sham group.¹³ Mean seizure frequency modeled using generalized estimating equations was significantly reduced in the treatment group compared with the sham group ($p=0.012$). During the blinded evaluation period, the mean seizure frequency in the treatment group was 22.4 (range, 0.0-226.8) and 29.8 (range, 0.3-44.46) in the sham group. The treatment group experienced a -37.9% change in seizure frequency (95% confidence interval [CI], -46.7% to -27.7%), while the sham group experienced a -17.3% change in seizure frequency (95% CI, -29.9% to -2.3%).

By the third month of the blinded evaluation period, the treatment group had 27% fewer days with seizures while the sham group experienced 16% fewer days ($p=0.048$). There were no significant differences between groups over the blinded evaluation period for secondary end points of responder rate (proportion of subjects who experienced a $\geq 50\%$ reduction in mean disabling seizure frequency vs the preimplant period), change in average frequency of disabling seizures, or change in seizure severity.

During the open-label period, subjects in the sham group demonstrated significant improvements in mean seizure frequency compared with the preimplant period ($p=0.04$). For all subjects (treatment and sham control), the responder rate at 1 year postimplant was 43%. Overall quality of life scores improved for both groups compared with baseline at 1 year ($p=0.001$) and 2 years postimplant ($p=0.016$).

For the study's primary safety end point, the significant adverse event rate over the first 28 days postimplant was 12%, which did not differ significantly from the prespecified literature-derived comparator of 15% for implantation of intracranial electrodes for seizure localization and epilepsy surgery. During the implant period and the blinded evaluation period, the significant adverse event rate was 18.3%, which did not differ significantly from the prespecified literature-derived comparator of 36% for implantation and treatment with deep brain stimulation for Parkinson disease. The treatment and sham groups did not differ significantly in terms of mild or serious adverse events during the blinded evaluation period. Intracranial hemorrhage occurred in 9 (4.7%) of 191 subjects; implant or incision site infection occurred in 10 (5.2%) of 191 subjects, and the devices were explanted from 4 of these subjects.

Follow-Up Analyses to the Pivotal Trial Subjects

In a follow-up to the RNS System Pivotal Trial, Heck et al (2014) compared outcomes at 1 and 2 years postimplant with baseline for patients in both groups (sham and control) who had the RNS stimulation device implanted during the RNS System Pivotal Trial.¹⁶ Of the 191 subjects implanted, 182 subjects completed follow-up to 1 year postimplant and 175 subjects completed follow-up to 2 years postimplant. Six patients withdrew from the trial, 4 underwent device explantation due to infection, and 5 died, with 1 due to sudden unexplained death in epilepsy. During the open-label period, at 2 years of follow-up, median percent reduction in seizures was 53% compared with the preimplant baseline ($p<0.001$), and the responder rate was 55%.

Loring et al (2015) analyzed one of the trial's prespecified safety end points (neuropsychologic function) during the trial's open-label period.¹⁷ Neuropsychological testing focused on language and verbal memory, measured by the Boston Naming Test and the Rey Auditory Verbal Learning Test. One hundred seventy-five subjects had cognitive assessment scores at baseline and at 1 or 2 years or both and were included in this analysis. The authors used reliable change indices (RCIs) to identify patients with changes in test scores beyond that attributed to practice effects or measurement error in the test-retest setting, with 90% RCIs used for classification. Overall, no significant group-level declines in any neuropsychological outcomes were detected. On the Boston Naming Test, 23.5% of subjects demonstrated RCI improvements while 6.7% had declines; on the Rey Auditory Verbal Learning Test, 6.9% of subjects demonstrated RCI improvements and 1.4% demonstrated declines.

Meador et al (2015) reported on quality of life and mood outcomes for individuals in the RNS pivotal trial.¹⁸ At the end of the blinded study period, both groups reported improvements in Quality of Life in Epilepsy Inventory-89 (QOLIE-89) scores, with no statistically significant differences between groups. In analysis of those with follow-up to 2 years postenrollment, implanted patients had statistically significant improvements in QOLIE-89 scores from enrollment to 1- and 2-year follow-up. Mood, as assessed by the Beck Depression Inventory and the Profile of Mood States, did not worsen over time.

Systematic Reviews

Cox et al (2014) reported on a systematic review of implantable neurostimulation devices, including RNS, along with vagus nerve stimulation and deep brain stimulation for refractory epilepsy.¹⁹ The evidence on RNS in this review was primarily from the pivotal RCT¹⁵, described previously. Reviewers concluded that RNS is "promising," but that improvements in the accuracy of the seizure prediction method and standardization of electrical stimulation parameters were needed.

Gooneratne et al (2016) performed a systematic review comparing neurostimulation technologies in refractory focal epilepsy.²⁰ They performed a literature search for studies with long-term efficacy data (≥ 5 years) and at least 30 patients evaluating vagus nerve stimulation, cortical responsive stimulation, or deep brain stimulation in refractory focal or focal epilepsy through November 2015. No direct comparisons of the technologies were found. The previously described pivotal trial of RNS was the only RNS study included. Indirect comparisons of the technologies were limited by differences in RCT inclusion criteria, definitions of response, and methods of data collection between studies. Reviewers concluded that all 3 neurostimulation technologies showed long-term efficacy, with progressively better seizure control over time.

Noncomparative Studies

Before and during conduct of the pivotal RCT to evaluate the RNS system, short- and long-term outcomes following the use of the device have been described in case series.

The Long-Term Treatment (LTT) Study was a 7-year, multicenter, prospective, open-label study to evaluate the RNS system's long-term efficacy and safety in individuals who participated in device's feasibility or pivotal trials. Bergey et al (2015) reported on follow-up for 191 participants in the LTT Study (of a total of 230 originally enrolled in the LTT Study) for a median 5.4 years.²¹ Of those who discontinued, 3 were lost to follow-up, 28 patients withdrew (9 to pursue other treatments, 5 due to insufficient efficacy, 5 decided not to replace the RNS system after expected battery depletion, 5 after infection resolved, 3 for noncompliance, 1 for elective explant, 1 due to ongoing suicidality/noncompliance), 4 underwent emergent explant, and 4 died. For follow-up at years 3 and 6, the median percent reductions in seizures were 60% and 66%, respectively. Statistically significant quality of life improved at 4 years, with a trend toward improvement at 5 years. The most common adverse events were implant site infection ($n=24$ [9.4%]) and increase in complex focal seizures ($n=20$ [7.8%]).

Since device approval, a single-center study by Lee et al (2015) has reported on outcomes after RNS implantation (40 surgeries) in 10 patients.²² In this series, 1 patient had an implant site infection requiring device explantation and another had multiple lead breakages.

Earlier studies have reported that the RNS implant was well-tolerated in small numbers of patients. Anderson et al (2008) reported on procedural details and clinical outcomes for 4 patients treated with the RNS device (as part of the device's pivotal clinical trial) and noted that the device implant was well-tolerated and qualitatively reduced the frequency of seizures.⁹ Kossoff et al (2004) reported qualitative reduction in seizure frequency in 4 patients with intractable seizures who received neurostimulation with an external RNS (a precursor to the FDA-approved implantable RNS device) during intracranial monitoring to localize seizure onset for surgery mapping.⁸

Cases in which chronic (i.e., not responsive to detected seizure activity) focal cortical stimulation was used to treat medically refractive epilepsy have also been described.²³ In these cases, cortical electrodes were placed during planned neurosurgical intervention for seizure mapping and were connected to a pulse generator.

Section Summary: RNS for Treatment of Refractory Focal Epilepsy

The most direct and rigorous evidence related to the effectiveness of RNS in the treatment of refractory focal seizures is from the RNS System Pivotal Trial, in which patients who had focal epilepsy refractory to at least 2 medications and received RNS treatment demonstrated a significantly greater reduction in their rates of seizures compared with sham-control patients. Although this single RCT was relatively small (97 patients in the treatment group), it was adequately powered for its primary outcome and all patients were treated with the device during the open-label period (97 in the original treatment group, 94 in the original sham group) and demonstrated a significant improvement in seizure rates compared with baseline. However, there were no differences in the percentage of patients who responded to RNS, and no

difference on most of the other secondary outcomes. Follow-up has been reported to 5 years postimplantation, without major increases in rates of adverse events.

Adverse Events with the RNS System

As a surgical procedure, implantation of the RNS system is associated with the risks that should be balanced against the risks of alternative treatments, including AEDs and other invasive treatments (vagal nerve stimulator and epilepsy surgery), and the risks of uncontrolled epilepsy. During the RNS System Pivotal Trial, rates of serious adverse events were relatively low: 3.7% of patients had implant site infections, 6% had lead revisions or damage, and 2.1% percent had intracranial hemorrhages during initial implantation.¹⁶

The FDA's summary of safety and effectiveness data for the RNS system summarized deaths and adverse events. As reported in the safety and effectiveness data, as of October 24, 2012, there were 11 deaths in the RNS System trials, including the pivotal trial and the ongoing long-term treatment study. Two of the deaths were suicides (one each in the pivotal and LTT studies), one due to lymphoma and another to complications of status epilepticus, and 7 were attributed to possible, probable, or definite sudden unexplained death in epilepsy. With 1195 patient implant years, the estimated sudden unexplained death in epilepsy rate is 5.9 per 1000 implant years, which is comparable with the expected rate for patients with refractory epilepsy.¹³

Additional safety outcomes have been reported to 5 years postimplantation through the device's LTT study (see above).

As of March 13, 2019, there were 203 reports in the FDA Manufacturer and User Facility Device Experience database for product code PFN. Five were labeled as event type "Malfunction," one was extended hospitalization due to aphasia, and all remaining reports were labeled as "Injury." Seven of the "Injury" event narratives mentioned hemorrhages, 3 stroke, 6 fluid leakage, 46 infection, 5 swelling or edema, and in 5 the device had become exposed.

Summary of Evidence

For individuals who have refractory focal epilepsy who receive RNS, the evidence includes an industry-sponsored RCT, which was used for Food and Drug Administration approval of the NeuroPace RNS System, as well as case series. Relevant outcomes are symptoms, morbid events, quality of life, and treatment-related mortality and morbidity. The pivotal trial was well-designed and well-conducted; it reported that RNS is associated with improvements in mean seizure frequency in patients with refractory focal epilepsy, with an absolute difference in change in seizure frequency of about 20% between groups, though the percentage of treatment responders with at least a 50% reduction in seizures did not differ from sham control. Overall, the results suggested a modest reduction in seizure frequency in a subset of patients. The number of adverse events reported in the available studies is low, although the data on adverse events were limited because small study samples. Generally, patients who are candidates for RNS are severely debilitated and have few other treatment options, so the benefits are likely high relative to the risks. In particular, patients who are not candidates for resective epilepsy surgery and have few treatment options may benefit from RNS. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests from Blue Cross Blue Shield Association, input was received from 2 specialty medical societies (3 responses) and 5 academic medical centers (4 responses) in 2014. There was consensus among reviewers that responsive neurostimulation is medically necessary

for patients with focal epilepsy with 1 to 2 foci who are not candidates for resective epilepsy surgery.

Practice Guidelines and Position Statements

In 2013, guidelines on vagus nerve stimulation (VNS) for the treatment of epilepsy were issued by the American Academy of Neurology.²⁴ The guidelines made the following recommendations: "VNS may be considered for seizures in children, for LSG [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). Children should be carefully monitored for site infection after VNS implantation." The Academy indicated that more information would be needed on the treatment of primary generalized epilepsy in adults (only 1 class II article addressed this population). The responsive neurostimulation system was not mentioned in these guidelines.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

An unpublished trial that might influence this review is shown in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02403843 ^a	RNS® System Post-Approval Study in Epilepsy	375	May 2023
NCT00572195	RNS® System Long-term Treatment (LTT) Clinical Investigation	230	May 2018 (terminated slow enrollment)

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

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Documentation for Clinical Review

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:
 - Seizure diagnosis (type and frequency over the past 3 months)
- Prior treatment(s) and response(s) including medical therapy
- Documented reason why focal resective epilepsy surgery is not an option
- Documentation of no contraindications for RNS placement

Post Service

- Procedure report(s)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

MN/IE

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

Type	Code	Description
CPT®	61850	Twist drill or burr hole(s) for implantation of neurostimulator electrodes, cortical
	61860	Craniectomy or craniotomy for implantation of neurostimulator electrodes, cerebral, cortical
	61863	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; first array
	61864	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; each additional array (List separately in addition to primary procedure)
	61880	Revision or removal of intracranial neurostimulator electrodes
	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
	61888	Revision or removal of cranial neurostimulator pulse generator or receiver
	95970	Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation,

Type	Code	Description
		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 (Code revision effective 1/1/2019)
	95971	Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with simple spinal cord or peripheral nerve (e.g., sacral nerve) neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional (Code revision effective 1/1/2019)
HCPCS	L8680	Implantable neurostimulator electrode, each
	L8686	Implantable neurostimulator pulse generator, single array, nonrechargeable, includes extension
	L8688	Implantable neurostimulator pulse generator, dual array, nonrechargeable, includes extension
ICD-10 Procedure	00H00MZ	Insertion of Neurostimulator Lead into Brain, Open Approach
	00H60MZ	Insertion of Neurostimulator Lead into Cerebral Ventricle, Open Approach

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
08/01/2016	BCBSA Medical Policy adoption	Medical Policy Committee
06/01/2017	Policy revision without position change	Medical Policy Committee
06/01/2018	Policy title change from Responsive Neurostimulation for the Treatment of Refractory Partial Epilepsy Policy revision without position change	Medical Policy Committee
07/01/2019	Policy revision without position change Coding update	Medical Policy Committee

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment,

procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)
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Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.