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

I. Responsive neurostimulation may be considered **medically necessary for individuals** with focal epilepsy who meet ALL of the following criteria:
   A. Are 18 years or older;
   B. Have a diagnosis of focal seizures with 1 or 2 well-localized seizure foci identified;
   C. 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;
   D. Are refractory to medical therapy (have failed ≥2 appropriate antiepileptic medications at therapeutic doses);
   E. Are not candidates for focal resective epilepsy surgery (e.g., have an epileptic focus near the eloquent cerebral cortex; have bilateral temporal epilepsy); and
   F. Do not have contraindications for responsive neurostimulation device placement (see Policy Guidelines section).

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

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

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

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- **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 indication[13,]:
"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."

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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.

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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 surgery[10,] or for identifying whether seizure foci are unilateral.[11,12,]

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

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 1 or more intended clinical use of the technology in the intended population

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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. Randomized controlled trials 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Clinical Context and Therapy 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 following PICO was used to select literature to inform this review.

Populations

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.

Note that the term focal seizure in older literature may be referred to as "partial seizure." The International League Against Epilepsy (2017) outlined updated terminology for seizure and epilepsy subtypes, dividing them into 3 groups: focal onset, generalized onset, and unknown onset.[13,] Focal-onset seizures are subdivided based on the associated level of consciousness, and subsequently into whether they are motor or non-motor-onset.

The International League Against Epilepsy defines drug-resistant epilepsy as epilepsy that has failed to achieve sustained freedom from seizures after adequate trials of 2 tolerated, appropriate, and used antiepileptic drugs (either alone or in combination).[14,] Epilepsy is drug-resistant in approximately 25% of newly diagnosed patients, and focal onset seizures have been found to be a risk factor.[15,]

Interventions

The therapy being considered is responsive neurostimulation. One device, the NeuroPace RNS System is currentlyOne device, the NeuroPace RNS System is currently approved by the U.S. Food and Drug Administration (FDA) and is commercially available. The system consists of an implantable neurostimulator, a cortical strip lead, impl. antable components and accessories, a tablet and telemetry wand, a patient data management system, a remote monitor for use by the patient to upload data to the data management system, and a magnet for patients to withhold therapy or to activate electrocorticograhic storage. The responsive neurostimulation stimulator and implant monitor the brain's electrical activity and deliver electrical stimulation when warranted. Before device implantation, the patient undergoes seizure localization, which includes inpatient video-

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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 testing (also referred to as 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.[16,]

Comparators

Because responsive neurostimulation 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 therapy, surgical management, other types of implanted stimulators (e.g., vagus nerve stimulation), 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-responsive neurostimulation treatment may also provide evidence about the efficacy of the responsive neurostimulation device.

Outcomes

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

Based on available literature, a minimum follow-up of 1 to 2 years is recommended, although 1 study followed patients for 7 years.

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

Review of Evidence

The body of evidence addressing whether responsive neurostimulation is associated with improved health outcomes for patients with focal epilepsy includes an industry-sponsored RCT, which was used for the device's FDA approval, as well as several published follow-up analyses.

RNS System Pivotal Study

Morrell et al (2011) reported on the RNS System Pivotal Study, a multicenter, double-blind , sham-controlled trial that served as the basis for the FDA's approval of the device.[17,] This RCT included 191 patients with medically intractable focal epilepsy who were implanted with the responsive neurostimulation 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, 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

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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 outcomes 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 (1 due to subject preference in the active stimulation group; 1 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.[12,] Mean seizure frequency modeled using generalized estimating equations was significantly reduced in the treatment group compared with the sham group (p=.012). During the blinded evaluation period, the mean seizure frequency in the treatment group was 22.4 (range, 0.0-226.8) compared with 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=.048). There were no significant differences between groups over the blinded evaluation period for secondary endpoints of responder rate (proportion of subjects who experienced a ≥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=.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=.001) and 2 years postimplant (p=.016).

For the study's primary safety endpoint, 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 RNS System Pivotal Study Subjects

Heck et al (2014) followed up on the RNS System Pivotal Study, comparing outcomes at 1 and 2 years post-implant with baseline for patients in both groups (sham and control) who had the responsive

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neurostimulation stimulation device implanted during the RNS System Pivotal Study.[18,] 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<.001), and the responder rate was 55%.

Loring et al (2015) analyzed one of the trial's prespecified safety endpoints (neuropsychologic function) during the trial's open-label period.[19,] 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 to identify patients with changes in test scores beyond that attributed to practice effects or measurement error in the test-retest setting, with 90% reliable change indices 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 reliable change index improvements while 6.7% had declines; on the Rey Auditory Verbal Learning Test, 6.9% of subjects demonstrated reliable change index improvements and 1.4% demonstrated declines.

Meador et al (2015) reported on quality of life and mood outcomes for individuals in the RNS System Pivotal Study.[20,] At the end of the blinded study period, both groups reported improvements in Quality of Life in Epilepsy Inventory-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 Quality of Life in Epilepsy Inventory-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.

Nair et al (2020) conducted a long-term, prospective, open-label study that included patients who participated in the 2-year feasibility or pivotal studies of the RNS System between 2004 and 2018. Patients were followed up for an additional 7 years.[21,] Overall, 230 patients enrolled in the study, and 162 completed all 9 years of follow-up, providing a total of 1895 patient-implantation years. Among 68 patients who discontinued the study, 4 experienced emergent explant, 5 were lost to follow-up, 9 were deceased, and 50 withdrew (5 transferred care to a nonstudy center, 7 were noncompliant, 8 experienced insufficient efficacy, 10 pursued other treatments, and 20 chose not to replace neurostimulator). The mean follow-up period was 7.5 years. At 9 years, the median percent reduction in seizure frequency was 75% (p<.0001), 73% of patients were considered responders, and 35% had at least 90% reduction in seizure frequency. Overall, 18.4% of patients experienced at least 1 year free of seizures. Overall scores for quality of life and epilepsy-targeted and cognitive domains of the Quality of Life in Epilepsy-89 inventory remained significantly improved at year 9 (p<.05). The only device-related serious adverse events that were reported in at least 5% of patients were implantation site infection and elective explantation of the neurostimulator, leads, or both. Overall, serious device-related implantation site infection occurred in 12.1% of patients. No serious adverse events occurred related to stimulation.

Section Summary: Responsive Neurostimulation for Treatment of Refractory Focal Epilepsy
The most direct and rigorous evidence related to the effectiveness of responsive neurostimulation in the treatment of refractory focal seizures is from the RNS System Pivotal Study, in which patients who had focal epilepsy refractory to at least 2 medications and received responsive neurostimulation 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 responsive

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neurostimulation, 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 Responsive Neurostimulation System

As a surgical procedure, implantation of the responsive neurostimulation system is associated with the risks that should be balanced against the risks of alternative treatments, including antiepileptic drugs and other invasive treatments (vagal nerve stimulator and epilepsy surgery), and the risks of uncontrolled epilepsy. During the RNS System Pivotal Study, 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.[18,]

The FDA's summary of safety and effectiveness data for the responsive neurostimulation 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 responsive neurostimulation system trials, including the RNS System Pivotal Study and the ongoing long-term treatment study. Two of the deaths were suicides (1 each in the pivotal and long-term treatment studies), 1 due to lymphoma, 1due 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.[12,]

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

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.No relevant clinical practice guidelines were identified.

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

A currently 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

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  o Type of seizure
- Frequency of seizures, particularly during the past 3 months
- Prior treatment(s) and response(s) including medical therapy and medication failures
- Documented reason why focal resective epilepsy surgery is not an option
- Documentation of no contraindications for RNS placement

Post Service (in addition to the above, please include the following):

- 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.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

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

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Type	Code	Description
	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
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

Policy History

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

Effective Date	Action
08/01/2016	BCBSA Medical Policy adoption
06/01/2017	Policy revision without position change
06/01/2018	Policy title change from Responsive Neurostimulation for the Treatment of Refractory Partial Epilepsy Policy revision without position change
07/01/2019	Policy revision without position change Coding update
06/01/2023	Policy reactivated. Previously archived from 06/01/2020 to 05/31/2023.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to

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treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

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 and Feedback (as applicable to your plan)

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 at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

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.

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Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
Reactivated Policy **Policy Statement:** N/A :	I. Responsive neurostimulation may be considered **medically necessary for individuals** with focal epilepsy who meet ALL of the following criteria: A. Are 18 years or older; B. Have a diagnosis of focal seizures with 1 or 2 well-localized seizure foci identified; C. 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; D. Are refractory to medical therapy (have failed ≥2 appropriate antiepileptic medications at therapeutic doses); E. Are not candidates for focal resective epilepsy surgery (e.g., have an epileptic focus near the eloquent cerebral cortex; have bilateral temporal epilepsy); and F. Do not have contraindications for responsive neurostimulation device placement (see Policy Guidelines section). II. Responsive neurostimulation is considered **investigational** for all other indications.

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