7.01.143	Responsive Neurostimulation for the Treatment of Refractory Focal Epilepsy		
Original Policy Date:	August 1, 2016	**Effective Date:**	June 1, 2024
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 greater than or equal to 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)
   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

See the Codes table for details.

Description

Approximately one-third of individuals with epilepsy do not respond to typical first-line therapy with antiepileptic medications. Seizures that occur in these individuals are referred to as refractory or drug-resistant. In individuals with refractory epilepsy, combination antiepileptic therapy often results in increased risk of adverse events. Other nonpharmacologic treatment options are available, including surgical approaches, ketogenic diet, and responsive neurostimulation. One responsive neurostimulation device, the NeuroPace RNS System, has U.S. Food and Drug Administration (FDA) 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[12,]:

> "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
Epilepsy Treatment

Medical Therapy for Focal Seizures
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. Standard therapy for seizures, including focal seizures, includes treatment with 1 or more of various antiepileptic drugs, which include newer antiepileptic drugs, such as oxcarbazepine, lamotrigine, topiramate, gabapentin, pregabalin, levetiracetam, tiagabine, and zonisamide.[1,] Currently, response to antiepileptic drugs is less than ideal: 1 systematic review comparing newer antiepileptic drugs for refractory focal epilepsy reported an overall average responder rate in treatment groups of 34.8%.[1,] As a result, a substantial number of individuals 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.[2,] 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 antiepileptic drugs.[3,] Selection of appropriate individuals for epilepsy surgery is important, because those with nonlesional extratemporal lobe epilepsy have worse outcomes after surgery than those with nonlesional

temporal lobe epilepsy.[4] Some individuals 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 has been widely used for refractory epilepsy, following U.S. Food and Drug Administration (FDA) approval of a vagus nerve stimulation device in 1997 and 2 randomized controlled trials evaluating vagus nerve stimulation in epilepsy.[5] Although the mechanism of action for vagus nerve stimulation is not fully understood, vagus nerve stimulation 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) 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. Deep brain stimulation 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 deep brain stimulation is not currently approved by FDA for stimulation of the anterior thalamic nucleus.[6] Stimulation of the cerebellar and hippocampal regions and the subthalamic, caudate, and centromedian nuclei have also been evaluated for the treatment of epilepsy.[5]

Responsive Neurostimulation for Epilepsy

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

Development of the responsive neurostimulation 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.[7] Individuals 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.[8] 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 responsive neurostimulation 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 FDA and is commercially available.

Responsive Neurostimulation for Seizure Monitoring

Although the intent of the electrocorticography component of the responsive neurostimulation 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 individuals' seizures. In particular, the seizure mapping data have been used for surgical planning of individuals who do not experience adequate seizure reduction with responsive neurostimulation placement. Several studies have described the use of responsive neurostimulation in evaluating seizure foci for epilepsy surgery[9] or for identifying whether seizure foci are unilateral.[10,11] This review does not further address use of responsive neurostimulation 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 individuals 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 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 individuals, 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 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, implantable components and accessories, a tablet and telemetry wand, an individual data management system, a remote monitor for use by the individual to upload data to the data management system, and a magnet for individuals 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 individual 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 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 individual through interrogation of the device with the telemetry wand and transmitted to the data management system.[16,]

Comparators
Because responsive neurostimulation is considered for individuals 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 individuals 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 individuals 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 individuals 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 or 2 epileptogenic foci. Thirty-two percent of those implanted had prior epilepsy surgery, and 34% had a prior vagal nerve stimulator.

Individuals were randomized to active stimulation (n=97) or sham stimulation (n=94). After the 4-week postoperative period, individuals 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 individual 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 individual 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 individuals 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 individuals 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 individuals in both groups (sham and control) who had the responsive 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 individuals 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 individuals 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 individuals 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 individuals who participated in the 2-year feasibility or pivotal studies of the RNS System between 2004 and 2018. Individuals were followed up for an additional 7 years.[21] Overall, 230 individuals enrolled in the study, and 162 completed all 9 years of follow-up, providing a total of 1895 individual-implantation years. Among 68 individuals 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 individuals were considered responders, and 35% had at least 90% reduction in seizure frequency. Overall, 18.4% of individuals 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 individuals were implantation site infection and elective explanation of the neurostimulator, leads, or both. Overall, serious device-related implantation site infection occurred in 12.1% of individuals. No serious adverse events occurred related to stimulation.

Systematic Reviews

Skrehot et al (2024) conducted a systematic review and meta-analysis of prospective and retrospective studies comparing the efficacy of different neurostimulation modalities, including vagus nerve stimulation, responsive neurostimulation, and deep brain stimulation for focal epilepsy.[22,] Literature was searched through November 2021. At 1 year follow-up, seizure reductions observed were 66.3% (95% CI: 52.7-79.8) for responsive neurostimulation (N=372; 5 studies) and 32.9% (95% CI: 14.9-51.0) for vagus nerve stimulation (N=61; 5 studies). At 2 years of follow-up, seizure reductions observed were 56.0% (95% CI: 44.7-67.3) for responsive neurostimulation (N=280; 4 studies) and 44.4% (95% CI: 28.9-60.0) for vagus nerve stimulation (N=42; 3 studies). At 3 years follow-up, seizure reductions observed were 68.4% (95% CI: 53.4-83.5) for responsive neurostimulation (N=261; 4 studies) and 53.5% (95% CI: 25.5-81.6) for vagus nerve stimulation (N=13; 1 study). The authors noted responsive neurostimulation studies had high heterogeneity and vagus nerve stimulation studies had low heterogeneity. Many of the studies were observational, non-randomized, and/or retrospective. Overall, the authors concluded the evidence suggests seizure reductions are greater for responsive neurostimulation compared to vagus nerve stimulation at one year post-implantation with diminishing differences in longer-term follow-up. Deep brain stimulation for epilepsy is addressed separately in Blue Shield of California Medical Policy: Deep Brain 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 individuals 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 individuals. Although this single RCT was relatively small (97 individuals in the treatment group), it was adequately powered for its primary outcome, and all individuals 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 individuals who responded to responsive 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 individuals had implant site infections, 6% had lead revisions or damage, and 2.1% 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, 1 due to complications of status epilepticus, and 7 were attributed to possible, probable, or definite sudden unexplained death in epilepsy. With 1195 individual-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 individuals 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	January 2026

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

References

1. Costa J, Fareleira F, Ascenção R, et al. Clinical comparability of the new antiepileptic drugs in refractory partial epilepsy: a systematic review and meta-analysis. Epilepsia. Jul 2011; 52(7): 1280-91. PMID 21729036
2. Wiebe S, Blume WT, Girvin JP, et al. A randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med. Aug 02 2001; 345(5): 311-8. PMID 11484687
3. de Tisi J, Bell GS, Peacock JL, et al. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. Lancet. Oct 15 2011; 378(9800): 1388-95. PMID 22000136
4. Noe K, Sulc V, Wong-Kisiel L, et al. Long-term outcomes after nonlesional extratemporal lobe epilepsy surgery. JAMA Neurol. Aug 2013; 70(8): 1003-8. PMID 23732844
5. Fridley J, Thomas JG, Navarro JC, et al. Brain stimulation for the treatment of epilepsy. Neurosurg Focus. Mar 2012; 32(3): E13. PMID 22380854
6. Fisher RS. Therapeutic devices for epilepsy. Ann Neurol. Feb 2012; 71(2): 157-68. PMID 22367987
7. Kossoff EH, Ritzl EK, Politsky JM, et al. Effect of an external responsive neurostimulator on seizures and electrographic discharges during subdural electrode monitoring. Epilepsia. Dec 2004; 45(12): 1560-7. PMID 15571514
8. Anderson WS, Kossoff EH, Bergey GK, et al. Implantation of a responsive neurostimulator device in patients with refractory epilepsy. Neurosurg Focus. Sep 2008; 25(3): E12. PMID 18759613

9. DiLorenzo DJ, Mangubat EZ, Rossi MA, et al. Chronic unlimited recording electrocorticography-guided resective epilepsy surgery: technology-enabled enhanced fidelity in seizure focus localization with improved surgical efficacy. J Neurosurg. Jun 2014; 120(6): 1402-14. PMID 24655096
10. King-Stephens D, Mirro E, Weber PB, et al. Lateralization of mesial temporal lobe epilepsy with chronic ambulatory electrocorticography. Epilepsia. Jun 2015; 56(6): 959-67. PMID 25988840
11. Spencer D, Gwinn R, Salinsky M, et al. Laterality and temporal distribution of seizures in patients with bitemporal independent seizures during a trial of responsive neurostimulation. Epilepsy Res. Feb 2011; 93(2-3): 221-5. PMID 21256715
12. Food and Drug Administration. Summary of Safety and Effectiveness Data: RNS System 2013; https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100026b.pdf. Accessed February 23, 2024.
13. Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia. Apr 2017; 58(4): 522-530. PMID 28276060
14. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. Jun 2010; 51(6): 1069-77. PMID 19889013
15. Xue-Ping W, Hai-Jiao W, Li-Na Z, et al. Risk factors for drug-resistant epilepsy: A systematic review and meta-analysis. Medicine (Baltimore). Jul 2019; 98(30): e16402. PMID 31348240
16. Neuropace, Inc. RNS(R) System Physician Manual for the RNS(R) Neurostimulator Model RNS-320. Revised February 2020. https://www.neuropace.com/wp-content/uploads/2021/02/neuropace-rns-system-manual-320.pdf. Accessed February 23, 2024.
17. Morrell MJ, King-Stephens D, Massey AD, et al. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology. Sep 27 2011; 77(13): 1295-304. PMID 21917777
18. Heck CN, King-Stephens D, Massey AD, et al. Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: final results of the RNS System Pivotal trial. Epilepsia. Mar 2014; 55(3): 432-41. PMID 24621228
19. Loring DW, Kapur R, Meador KJ, et al. Differential neuropsychological outcomes following targeted responsive neurostimulation for partial-onset epilepsy. Epilepsia. Nov 2015; 56(11): 1836-44. PMID 26385758
20. Meador KJ, Kapur R, Loring DW, et al. Quality of life and mood in patients with medically intractable epilepsy treated with targeted responsive neurostimulation. Epilepsy Behav. Apr 2015; 45: 242-7. PMID 25819949
21. Nair DR, Laxer KD, Weber PB, et al. Nine-year prospective efficacy and safety of brain-responsive neurostimulation for focal epilepsy. Neurology. Sep 01 2020; 95(9): e1244-e1256. PMID 32690786
22. Skrehot HC, Englot DJ, Haneef Z. Neuro-stimulation in focal epilepsy: A systematic review and meta-analysis. Epilepsy Behav. May 2023; 142: 109182. PMID 36972642

Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - 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
	61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
	61888	Revision or removal of cranial neurostimulator pulse generator or receiver
	61889	Insertion of skull-mounted cranial neurostimulator pulse generator or receiver, including craniectomy or craniotomy, when performed, with direct or inductive coupling, with connection to depth and/or cortical strip electrode array(s) ***(Code effective 01/01/2024)***
	61891	Revision or replacement of skull-mounted cranial neurostimulator pulse generator or receiver with connection to depth and/or cortical strip electrode array(s) ***(Code effective 01/01/2024)***
	61892	Removal of skull-mounted cranial neurostimulator pulse generator or receiver with cranioplasty, when performed ***(Code effective 01/01/2024)***
	95836	Electrocorticogram from an implanted brain neurostimulator pulse generator/transmitter, including recording, with interpretation and written report, up to 30 days
	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,

Type	Code	Description
		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.
03/01/2024	Coding update
06/01/2024	Annual review. No change to policy statement. Policy guidelines and literature review updated. Coding update.

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 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.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	AFTER
Responsive Neurostimulation for the Treatment of Refractory Focal Epilepsy 7.01.143 **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.	**Responsive Neurostimulation for the Treatment of Refractory Focal Epilepsy 7.01.143** **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 greater than or equal to 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) F. Do not have contraindications for responsive neurostimulation device placement (see Policy Guidelines section) II. Responsive neurostimulation is considered **investigational** for all other indications.