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Responsive Neurostimulation for the Treatment of Refractory Focal Epilepsy

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Related Policies (if applicable)
None

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Coverage

Responsive neurostimulation **may be considered medically necessary** for individuals with focal epilepsy who meet **ALL** of the following criteria:

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

Responsive neurostimulation **is considered experimental investigational and/or unproven** for all other indications.

Policy Guidelines

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

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.

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 non-lesional extratemporal lobe epilepsy have worse outcomes after surgery than those with non-lesional 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.

<u>Neurostimulation for Neurologic Disorders</u>
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 [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 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 DBS 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 DBS 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 the 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 the 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 policy does not further address use of responsive neurostimulation exclusively for seizure monitoring.

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 2 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 3 most recent months (with no month with fewer than 2 seizures) and has not been evaluated in patients with less frequent seizures."

FDA product code: PFN.

Rationale

Medical policies 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.

Responsive Neurostimulation for Treatment of Refractory Focal Epilepsy

<u>Clinical Context and Therapy Purpose</u>

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 policy.

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 electrocorticographic 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 [VNS]), 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.

<u>Study Selection Criteria</u>

Methodologically credible studies were selected using the following principles:

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

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.

<u>RNS System Pivotal Study</u>

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.

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 to 295) and 34.9 (range, 3 to 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 to 226.8) compared with 29.8 (range, 0.3 to 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 (DBS) 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.

<u>Follow-Up Analyses to the RNS System Pivotal Study Subjects</u>
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 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 an analysis of those with follow-up to 2 years post-enrollment, 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 a 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.

<u>Systematic Reviews</u>
Skrehot et al. (2024) conducted a systematic review and meta-analysis of prospective and retrospective studies comparing the efficacy of different neurostimulation modalities, including VNS, responsive neurostimulation, and DBS for focal epilepsy. Literature was searched through November 2021. (22) At 1 year follow-up, seizure reductions observed were 66.3% (95% CI: 52.7 to 79.8) for responsive neurostimulation (N=372; 5 studies) and 32.9% (95% CI: 14.9 to 51.0) for VNS (N=61; 5 studies). At 2 years of follow-up, seizure reductions observed were

56.0% (95% CI: 44.7 to 67.3) for responsive neurostimulation (N=280; 4 studies) and 44.4% (95% CI: 28.9 to 60.0) for VNS (N=42; 3 studies). At 3 years follow-up, seizure reductions observed were 68.4% (95% CI: 53.4 to 83.5) for responsive neurostimulation (N=261; 4 studies) and 53.5% (95% CI: 25.5 to 81.6) for VNS (N=13; 1 study). The authors noted responsive neurostimulation studies had high heterogeneity and VNS 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 VNS at 1-year post-implantation with diminishing differences in longer-term follow-up.

Shi et al. (2025) conducted a systematic review and meta-analysis of RCTs, open-label extension and prospective studies comparing the efficacy of surgical excision, neuromodulation interventions, including DBS, responsive neurostimulation, VNS, transcutaneous auricular non-vagal nerve stimulation, and other investigational modalities for individuals with drug-resistant epilepsy. (23) Literature was reviewed through April 2024. To ensure a robust and comprehensive analysis, this review was bifurcated into 2 distinct segments, Bayesian network meta-analysis (NMA), which incorporated RCTs exclusively, and a single-arm meta-analysis (SMA) that included RCTs, associated open-label extension and prospective studies to assess the mean seizure frequency reduction as expressed via odds ratio (OR). The NMA reported an OR of 1.55 (95% CI: 0.77 to 3.10) for responsive neurostimulation (N=97; 1 study), 1.23 (95% CI: 0.69 to 2.22) for transcutaneous auricular VNS (N=201; 3 studies), 1.17 (95% CI: 0.59 to 2.28) for invasive VNS (N=94; 1 study), and 0.86 (95% CI: 0.35 to 2.16) for transcutaneous auricular non-vagal nerve stimulation (N=46; 1 study) as compared to anti-seizure medications. The SMA reported an OR of 2.37 (95% CI: 2.09 to 2.7) for responsive neurostimulation (N=1190 [reported as person-times]; 6 studies), 1.83 (95% CI: 1.58 to 2.13) for invasive VNS (N=1337 [reported as person-times]; 5 studies), and 1.73 (95% CI: 1.06 to 2.83) for transcutaneous auricular VNS (N=201 [reported as person-times]; 3 studies) when comparing post-treatment versus pretreatment outcomes. SMA further explored these outcomes and stratified them into a short-term (year 1; n=1956; 22 studies), medium-term (year 2; n=1008; 7 studies), and long-term (year 3; n=1022; 8 studies) cohorts. The short-term efficacy cohort reported an OR of 1.68 (95% CI: 1.65 to 1.72) for responsive neurostimulation (n=278; 2 studies), 1.62 (95% CI: 1.36 to 1.93) for invasive VNS (n=621; 4 studies), and 1.73 (95% CI: 1.11 to 2.71) for transcutaneous auricular VNS (n=201; 3 studies). The medium-term efficacy cohort reported an OR of 2.04 (95% CI: 1.93 to 2.17) for responsive neurostimulation (n= 390; 3 studies) and 1.86 (95% CI: 1.69 to 2.04) for invasive VNS (n=348; 1 study), while the long-term efficacy cohort reported an OR of 3.65 (95% CI: 2.66 to 5.00) for responsive neurostimulation (n=522; 4 studies) and 2.84 (95% CI: 1.55 to 5.18) for invasive VNS (n=368; 2 studies). Of note, both the NMA and SMA include all types of drug-resistant epileptic patients and do not report data for refractory focal epilepsy, exclusively. Additionally, the limited number of studies for both analyses reduces the generalizability of these findings. Other limitations include potential bias within the SMA due to a lack of blinding, variability in follow-up, and a lack of controls. Overall, the authors concluded that the evidence suggests seizure reductions are greater for responsive neurostimulation compared to VNS at 1-, 2-, and 3-year post-implantation with a durable response in longer-term follow-up.

DBS for epilepsy is addressed separately in medical policy SUR712.025.

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 differences 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 post-implantation through the device's long-term treatment study (see above).

Summary of Evidence
For individuals who have refractory focal epilepsy who receive responsive neurostimulation, the evidence includes an industry-sponsored randomized controlled trial (RCT), which was used for Food and Drug Administration (FDA) approval of the NeuroPace RNS System, as well as several published follow-up analyses. Relevant outcomes are symptoms, morbid events, quality of life, and treatment-related mortality and morbidity. The RCT was well-designed and well-

conducted; it reported that responsive neurostimulation is associated with improvements in mean seizure frequency in individuals with refractory focal epilepsy, with an absolute difference in change in seizure frequency of about 20% between groups; however, the percentage of treatment responders with at least a 50% reduction in seizures did not differ from sham control. Overall, the results suggested a modest reduction in seizure frequency in a subset of individuals. The number of adverse events reported in the available studies is low, although the data on adverse events were limited because of small study samples. Generally, individuals who are candidates for responsive neurostimulation are severely debilitated and have few other treatment options, so the benefits are likely high relative to the risks. In particular, individuals who are not candidates for resective epilepsy surgery and have few treatment options may benefit from responsive neurostimulation. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements
No relevant clinical practice guidelines were identified.

Ongoing and Unpublished Clinical Trials
Currently ongoing and/or unpublished trials that might influence this policy are shown in Table 1.

Table 1. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
NCT02403843[a]	RNS System Post-Approval Study in Epilepsy	375	Jan 2026
NCT04839601[a]	RNS System RESPONSE Study	200	Dec 2027

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

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

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

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

CPT Codes	61850, 61860, 61863, 61864, 61880, 61885, 61886, 61888, 61889, 61891, 61892, 95836, 95970, 95971
HCPCS Codes	C1767, L8680, L8686, L8688

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Centers for Medicare and Medicaid Services (CMS)

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

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

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

Policy History/Revision

Date	Description of Change
12/01/2025	Document updated. The following change was made to Coverage: Moved language on contraindications for responsive neurostimulation device placement to Policy Guidelines section. Added reference 23.
09/15/2024	Document updated with literature review. Coverage unchanged. Added reference 22; others removed.

01/01/2024	Reviewed. No changes.
09/15/2022	Document updated with literature review. Coverage unchanged. Added references 23-24. Document title changed from: Responsive Neurostimulation (RNS) for the Treatment of Refractory Focal Epilepsy.
08/01/2021	Reviewed. No changes.
12/15/2020	Document updated with literature review. Coverage unchanged. Added/updated the following references: 14-16.
08/01/2019	Reviewed. No changes.
08/15/2018	Document updated with literature review. The following change(s) were made to Coverage: Term “partial epilepsy” changed to “focal epilepsy”. No references added. Title changed from: Responsive Neurostimulation (RNS) for the Treatment of Refractory Partial Epilepsy.
08/15/2017	Document updated with literature review. Coverage unchanged.
09/01/2016	Reviewed. No changes.
08/01/2015	New medical document. 1) Responsive neurostimulation may be considered medically necessary for patients with partial epilepsy who meet all of the following criteria: 18 years or older, have a diagnosis of partial-onset seizures with 1 or 2 well-localized seizure foci identified, have an average of 3 or more disabling seizures (e.g., motor partial seizures, complex partial seizures, or secondary generalized seizures) per month over the prior 3 months, are refractory to medical therapy (have failed 2 or more appropriate antiepileptic medications at therapeutic doses), are not candidates for focal resective epilepsy surgery (e.g., have an epileptic focus near eloquent cerebral cortex; have bilateral temporal epilepsy), and do not have any of the following contraindications for RNS placement: three or more specific seizure foci, presence of primary generalized epilepsy, or presence of a rapidly progressive neurologic disorder. 2) RNS is considered experimental investigational and/or unproven for all other indications.