Regence

**Medical Policy Manual** Surgery, Policy No. 216

# *Responsive Neurostimulation*

**Effective**: March 1, 2024

**Next Review:** September 2024
**Last Review:** January 2024

## IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

## DESCRIPTION

Responsive neurostimulation (RNS) provides cortical stimulation in response to detection of specific seizure-related electrical signals. RNS 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. RNS is used in individuals with refractory focal epilepsies to provide a treatment option that is an alternative to or an improvement on existing therapies.

## MEDICAL POLICY CRITERIA

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

   A. 18 years or older; and

   B. Device is FDA approved (PMA or 510k only); and

   C. Diagnosis of focal seizures with 1 or 2 localized seizure foci identified; and

   D. Average of 3 or more disabling seizures (e.g., motor focal seizures, complex focal seizures, or secondary generalized seizures) per month for 3 consecutive months; and

   E. Failed greater than or equal to 2 antiepileptic medications; and

F. Not a candidate for focal resective epilepsy surgery (e.g., have an epileptic focus near the eloquent cerebral cortex; have bilateral temporal epilepsy); and

G. Do not have any of the following contraindications for responsive neurostimulation device placement:

1. 3 or more specific seizure foci
2. Presence of primary generalized epilepsy
3. Presence of a rapidly progressive neurologic disorder

II. Responsive neurostimulator revision(s) or replacement(s) may be considered **medically necessary** after the device has been placed.

III. Responsive neurostimulation is considered **investigational** for all other indications, including but not limited to patients with focal epilepsy who do not meet the above Criteria.

*NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.*

## LIST OF INFORMATION NEEDED FOR REVIEW

**REQUIRED DOCUMENTATION:**

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical exam, including requirements as outlined by the policy criteria
- Number of seizure foci
- Documentation of seizure occurrence over the prior 3 months
- Clinical documentation demonstrating medicine-refractory symptoms
- Clinical documentation demonstrating that the patient is not a candidate for focal resective epilepsy surgery
- Presence of other conditions, such as a neurological disorder

## CROSS REFERENCES

1. Vagus Nerve Stimulation, Surgery, Policy No. 74
2. Deep Brain Stimulation, Surgery, Policy No. 84
3. Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy of Intracranial, Skull Base, and Orbital Sites, Surgery, Policy No. 213

## BACKGROUND

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 two 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: one 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 five-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 two randomized controlled trials evaluating VNS in epilepsy.[6] Although the mechanism of action for VNS is not fully understood, VNS is thought to reduce seizure activity through activation of vagal visceral afferents with diffuse central nervous system projections, leading to a widespread effect on neuronal excitability.

Stimulation of other locations in the neuroaxis has been studied for a variety of neurologic disorders. Electrical stimulation of deep brain nuclei (deep brain stimulation [DBS]) involves the use of chronic, continuous stimulation of a target. It has been most widely used in the treatment of Parkinson disease and other movement disorders, and has been investigated for treating epilepsy. DBS of the anterior thalamic nuclei was studied in a randomized control trial, the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy trial, but DBS is not currently approved by 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 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.

## REGULATORY STATUS

In November 2013, the NeuroPace RNS® System (NeuroPace) was approved by 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 two 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 three 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.

## EVIDENCE SUMMARY

### RNS FOR TREATMENT OF REFRACTORY FOCAL EPILEPSY

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

#### Pivotal Trial

RNS for epilepsy was evaluated in the RNS System Pivotal Trial, a multicenter, double-blinded, sham-controlled trial that served as the basis of FDA's approval of the device.[14] Published by Morrell (2011), this RCT included 191 patients with medically intractable focal epilepsy who were implanted with the RNS device and randomized to treatment or sham control after a one-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 two trials of antiepileptic drugs (AEDs), who had at least three disabling seizures (motor focal seizures, complex focal seizures, or secondary generalized seizures) per month on average, and who had standard diagnostic testing that localized one or two 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 four-week postoperative period, patients received either sham or active stimulation according to group assignment. There was a four-week stimulation optimization period, followed by a three-month blinded evaluation period. In the evaluation period, all outcome data were gathered by a physician blinded to group assignment, and the neurostimulator was managed by a nonblinded physician. One patient in each group did not complete the stimulus optimization period (one due to subject preference in the active stimulation group; one due to death in the sham stimulation group). An additional patient in each group did not complete the blinded evaluation phase due to emergent explant of the device. After the three-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 (five due to death, two to emergent explant, four 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, 3-338) in the sham group.[13] Mean seizure frequency modeled using generalized estimating equations was significantly reduced in the treatment group compared with the sham group (p=0.012). During the blinded evaluation period, the mean seizure frequency in the treatment group was 22.4 (range 0.0 to 227) and 29.8 (range 0.3 to 447) in the sham group. The treatment group experienced a -37.9% change in seizure frequency (95% confidence

interval [CI] -46.7% to -27.7%), while the sham group experienced a -17.3% change in seizure frequency (95% CI -29.9% to -2.3%).

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

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

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

**Follow-Up Analyses to the Pivotal Trial Subjects**

In a follow-up to the RNS System Pivotal Trial, Heck (2014) compared outcomes at one and two years postimplant with baseline for patients in both groups (sham and control) who had the RNS stimulation device implanted during the RNS System Pivotal Trial.[15] Of the 191 subjects implanted, 182 subjects completed follow-up to one year postimplant and 175 subjects completed follow-up to two years postimplant. Six patients withdrew from the trial, four underwent device explantation due to infection, and five died, with one due to sudden unexplained death in epilepsy. During the open-label period, at two years of follow-up, median percent reduction in seizures was 53% compared with the preimplant baseline (p<0.001), and the responder rate was 55%.

Loring (2015) analyzed one of the trial's prespecified safety end points (neuropsychologic function) during the trial's open-label period.[16] 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 one or two years or both and were included in this analysis. The authors used reliable change indices (RCIs) to identify patients with changes in test scores beyond that attributed to practice effects or measurement error in the test-retest setting, with 90% RCIs used for classification. Overall, no significant group-level declines in any neuropsychological outcomes were detected. On the Boston Naming Test, 23.5% of subjects demonstrated RCI improvements while 6.7% had declines; on the Rey Auditory Verbal Learning Test, 6.9% of subjects demonstrated RCI improvements and 1.4% demonstrated declines.

Meador (2015) reported on quality of life and mood outcomes for individuals in the RNS pivotal trial.[17] At the end of the blinded study period, both groups reported improvements in Quality of Life in Epilepsy Inventory-89 (QOLIE-89) scores, with no statistically significant differences between groups. In analysis of those with follow-up to two years post-enrollment, implanted patients had statistically significant improvements in QOLIE-89 scores from enrollment to one- and two-year follow-up. Mood, as assessed by the Beck Depression Inventory and the Profile of Mood States, did not worsen over time.

Nair (2020) published a long-term prospective open-label study that included patients who participated in the two-year feasibility or pivotal studies of the RNS® System between 2004 and 2018.[18] Patients were followed for an additional seven years. Overall, 230 patients enrolled in the study and 162 completed all nine years of follow-up, providing a total of 1,895 patient-implantation years. Among 68 patients who discontinued the study, four experienced emergent explant, five were lost to follow up, nine were deceased, and 50 withdrew (five transferred care to a non-study center, seven were noncompliant, eight experienced insufficient efficacy, 10 pursued other treatments, and 20 chose not to replace neurostimulator). The mean follow-up period was 7.5 years. At nine years, the median percent reduction in seizure frequency was 75% ($p<0.0001$), 73% of patients were considered responders, and 35% had a ≥90% reduction in seizure frequency. Overall, 18.4% of patients experienced at least one year free of seizures. Overall scores for quality of life and epilepsy-targeted and cognitive domains of the Quality of Life in Epilepsy-89 (QOLIE-89) inventory remained significantly improved at year nine ($p<0.05$). The only device-related serious adverse events that were reported in ≥ 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: RNS for Treatment of Refractory Focal Epilepsy

The most direct and rigorous evidence related to the effectiveness of RNS in the treatment of refractory focal seizures is from the RNS System Pivotal Trial, in which patients who had focal epilepsy refractory to at least two medications and received RNS treatment demonstrated a significantly greater reduction in their rates of seizures compared with sham-control patients. Although this single RCT was relatively small (97 patients in the treatment group), it was adequately powered for its primary outcome and all patients were treated with the device during the open-label period (97 in the original treatment group, 94 in the original sham group) and demonstrated a significant improvement in seizure rates compared with baseline. However, there were no differences in the percentage of patients who responded to RNS, and no difference on most of the other secondary outcomes. Follow-up has been reported to five years postimplantation, without major increases in rates of adverse events.

### Adverse Events with the RNS System

As a surgical procedure, implantation of the RNS system is associated with the risks that should be balanced against the risks of alternative treatments, including AEDs and other invasive treatments (vagal nerve stimulator and epilepsy surgery), and the risks of uncontrolled epilepsy. During the RNS System Pivotal Trial, rates of serious adverse events were relatively low: 3.7% of patients had implant site infections, 6% had lead revisions or damage, and 2.1% percent had intracranial hemorrhages during initial implantation.[15]

FDA's summary of safety and effectiveness data for the RNS system summarized deaths and adverse events. As reported in the safety and effectiveness data, as of October 24, 2012, there were 11 deaths in the RNS System trials, including the pivotal trial and the ongoing long-term treatment study. Two of the deaths were suicides (one each in the pivotal and LTT studies), one due to lymphoma and another to complications of status epilepticus, and seven 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 refectory epilepsy.[13]

The Long-Term Treatment (LTT) Study was a seven-year, multicenter, prospective, open-label study to evaluate the RNS system's long-term efficacy and safety in individuals who participated in device's feasibility or pivotal trials. Bergey (2015) reported on follow-up for 191 participants in the LTT Study (of a total of 230 originally enrolled in the LTT Study) for a median 5.4 years.[19] Of those who discontinued, three were lost to follow-up, 28 patients withdrew (nine to pursue other treatments, five due to insufficient efficacy, five decided not to replace the RNS system after expected battery depletion, five after infection resolved, three for noncompliance, one for elective explant, one due to ongoing suicidality/noncompliance), four underwent emergent explant, and four died. For follow-up at years three and six, the median percent reductions in seizures were 60% and 66%, respectively. Statistically significant quality of life improved at four years, with a trend toward improvement at five years. The most common adverse events were implant site infection (n=24 [9.4%]) and increase in complex focal seizures (n=20 [7.8%]).

### Summary of Evidence

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

## PRACTICE GUIDELINE SUMMARY

The American Academy of Neurology has published guidelines on specific treatments for epilepsy, which were reaffirmed in 2019.[20] It has not published any guidelines with recommendations regarding responsive neurostimulation.

## SUMMARY

It appears that in patients with refractory focal epilepsy, responsive neurostimulation (RNS) may improve health outcomes, including a reduction in seizure frequency in some patients. In particular, patients who are not candidates for resective epilepsy surgery and have few treatment options may benefit from RNS. Therefore, RNS may be considered medically necessary in patients with medication-refractory focal epilepsy when criteria are met.

In certain situations, a responsive neurostimulation device may no longer be able to perform its basic function due to damage or wear. When a stimulator is out of its warranty period and cannot be repaired adequately to meet the patient's medical needs, replacement of the device may be medically appropriate. Therefore, responsive neurostimulator revision(s) or replacement(s) may be considered medically necessary after the device has been placed.

There is not enough research to show that responsive neurostimulation (RNS) improves health outcomes for all other indications not meeting the criteria, including but not limited to patients with focal epilepsy who do not meet the criteria. Therefore, RNS is considered investigational when criteria are not met.

## REFERENCES


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## CODES

| Codes | Number | 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 (eg, thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; first array |
| | 61864 | ;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 | ;with connection to 2 or more electrode arrays |
| | 61888 | Revision or removal of cranial neurostimulator pulse generator or receiver |

| Codes | Number | Description |
|---|---|---|
| | 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) |
| | 61891 | Revision or replacement of skull-mounted cranial neurostimulator pulse generator or receiver with connection to depth and/or cortical strip electrode array(s) |
| | 95970 | Electronic analysis of implanted neurostimulator pulse generator system (eg, rate, pulse amplitude, pulse duration, configuration of wave form, battery status, electrode selectability, output modulation, cycling, impedance and patient compliance measurements); simple or complex brain, spinal cord, or peripheral (ie, cranial nerve, peripheral nerve, sacral nerve, neuromuscular) neurostimulator pulse generator/transmitter, without reprogramming |
| | 95971 | ;simple spinal cord, or peripheral (ie, peripheral nerve, sacral nerve, neuromuscular) neurostimulator pulse generator/transmitter, with intraoperative or subsequent programming |
| HCPCS | L8678 | Electrical stimulator supplies (external) for use with implantable neurostimulator, per month |
| | L8680 | Implantable neurostimulator electrode, each |
| | L8686 | Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension |
| | L8688 | Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension |

***Date of Origin:*** *September 2019*