Responsive Neurostimulation for the Treatment of Refractory Partial Epilepsy

Summary

Responsive neurostimulation (RNS) for the treatment of epilepsy involves the use of 1 or more implantable electric leads that serve both a seizure detection and neurostimulation function. The device is programmed using a proprietary algorithm to recognize seizure patterns from electrocorticography output and to deliver electrical stimulation with the goal of terminating a seizure. One device, the Neuropace RNS System, has U.S. Food and Drug Administration (FDA) approval for the treatment of refractory partial epilepsy.

The available literature related to the efficacy of RNS for partial epilepsy consists of 1 industry-sponsored randomized controlled trial (RCT), which was used for the device’s FDA approval, with 2-year follow up available. In addition, there were several case series and case reports. The available RCT is well-designed and reported that RNS is associated with improvements in mean seizure frequency in patients with refractory partial epilepsy, with an absolute difference in change in seizure frequency of about 20% (approximately 5 seizures per month) between groups, but that the percent of patients who responded to treatment with at least a 50% reduction in seizures was not different from sham control. The number of adverse events reported in the available studies is low. Although the data on adverse events is limited by small numbers of patients, and follow-up beyond 2 years has not been reported, patients who are candidates for RNS are generally severely debilitated, and have limited other treatment options. Therefore, RNS may be considered medically necessary in patients with medication-refractory partial epilepsy who are not candidates for epilepsy surgery, as outlined in the policy statement.

Related Policies

7.01.20 Vagus Nerve Stimulation
7.01.63 Deep Brain Stimulation

Policy

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Responsive neurostimulation may be considered medically necessary for patients with partial epilepsy who meet ALL of the following criteria:
- Are 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).
- Do not have contraindications for RNS placement (see “Policy Guidelines”).

Responsive neurostimulation is considered **not medically necessary** for all other indications.

### Policy Guidelines

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

### Background

#### Overview of Seizures and Seizure Disorders

Partial seizures arise from a discrete area of the brain and can cause a range of different symptoms, depending on the seizure type and the brain area involved. Partial seizures may be further grouped into simple partial seizures, which may be associated with motor, sensory, or autonomic symptoms, or complex partial seizures, in which patients’ consciousness is affected. Complex partial seizures may be associated with abnormal movements (automatisms). In some cases, partial seizures may result in secondary generalization, in which widespread brain electrical activity occurs after the onset of a partial seizure, thereby resulting in a generalized seizure.

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 (EEG), associated clinical or neuroimaging findings, and genetic factors. Temporal lobe epilepsy is the most common syndrome associated with partial-onset seizures. Thirty percent to 40% of those with partial-onset seizures have intractable epilepsy, defined as a failure to control seizures after 2 seizure medications that have been appropriately chosen and used.¹

### Epilepsy Treatment

**Medical Therapy for Seizures**

Standard therapy for seizures, including partial seizures, includes treatment with 1 or more of variety of antiepileptic drugs (AEDs). Advances have occurred with the development and approval of newer AEDs, including oxcarbazepine, lamotrigine, topiramate, gabapentin, pregabalin, levetiracetam, tiagabine, and zonisamide.² However, response to AEDs is less than ideal: 1 systematic review of comparisons between multiple newer AEDs for refractory partial epilepsy reported an overall average
responder rate in the treatment groups of 34.8%. As a result, there are substantial numbers of patients who 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, 1 RCT demonstrated that surgery for epilepsy was superior to prolonged medical therapy in reducing seizures associated with impaired awareness and in improving quality of life. Surgery for refractory focal epilepsy (excluding simple partial seizures) is associated with 5-year rates of freedom from seizures of 52%, with 28% of seizure-free individuals able to discontinue AEDs. Selection of appropriate patients for epilepsy surgery is important, as those with nonlesional extratemporal lobe epilepsy have worse outcomes after surgery than those with nonlesional temporal lobe epilepsy. 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 neurological deficit.

**Neurostimulation for Neurologic Disorders**

Electrical stimulation at one of several locations has been used as therapy for epilepsy, either in addition to or as an alternative to medical or surgical therapy. Vagus nerve stimulation (VNS) has been widely used for refractory epilepsy, following FDA approval of a VNS device in 1997 and 2 RCTs evaluating VNS in epilepsy. Although the mechanism of the VNS’s therapeutic effects are not fully understood, VNS is thought 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 at deep brain nuclei (deep brain stimulation [DBS]) involves the use of chronic, continuous stimulation of a target, and has been most widely used in the treatment of Parkinson disease and other movement disorders, but has also been investigated for epilepsy. DBS of the anterior thalamic nuclei has been studied in 1 RCT, the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) trial, but DBS is not currently approved by FDA for stimulation of the anterior thalamic nucleus. Stimulation of the cerebellar and hippocampal regions and the subthalamic, caudate, and centromedian nuclei have also been evaluated for the treatment of epilepsy.

**RNS for Epilepsy**

RNS shares some features with DBS, but is differentiated by its use of direct cortical stimulation and by the fact that the device performs both monitoring and stimulation functions. The RNS system provides stimulation in response to detection of specific epileptiform patterns, while DBS provides continuous or intermittent stimulation at pre-programmed settings.

Development of the RNS system arose out of 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. 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.\textsuperscript{9}

In tandem with the recognition that cortical stimulation may be able to stop epileptiform discharges was the development of fast pre-ictal seizure prediction algorithms. These algorithms involve the interpretation of electrocorticographic data from detection leads 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 to attempt to halt a detected epileptiform discharge.

One system, the Neuropace RNS® System, is currently approved by FDA and is commercially available. The system consists of an implantable neurostimulator, a cortical strip lead, a depth lead, a programmer and telemetry wand, and a patient data management system. Before device implantation, the patient undergoes seizure localization, which includes inpatient video-EEG monitoring and magnetic resonance imaging for detection of epileptogenic lesions. Additional testing may also include EEG with intracranial electrodes, intraoperative or extraoperative stimulation with subdural electrodes, additional imaging studies, and/or neuropsychological testing and intracarotid amytal (Wada) testing. The selection and location of the leads are based on the location of seizure foci. Cortical strip leads are recommended for seizure foci on the cortical surface, while the depth leads are recommended for seizure foci beneath the cortical surface. The implantable neurostimulator and cortical and/or depth leads are implanted intracranially. The neurostimulator is initially programmed in the operating room to detect electrocorticographic activity. Responsive therapy is initially set up using standard parameters (Neuropace recommended initial settings: frequency 200 Hz; pulse width 160 μs; burst duration 100 ms; current 1.0 mA) from the electrodes from which electrical activity is detected. Over time, the responsive stimulation settings are adjusted on the basis of electrocorticography data, which are collected by the patient through interrogation of the device with the telemetry wand and transmitted to the data management system.\textsuperscript{10}

**Regulatory Status**

In November 2013, the NeuroPace RNS® System (Neuropace Inc., Mountain View, CA) was approved by FDA through the premarket approval process for the following indication\textsuperscript{11}:

“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**

Assessment of efficacy for therapeutic intervention involves a determination of whether the intervention improves health outcomes. The optimal study design for this purpose is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. Intermediate outcome measures may also be adequate if there is an established link between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes provide useful information on health outcomes, but are prone to biases such as noncomparability of treatment groups, placebo effect, and variable natural history of the condition.

For the evaluation of responsive neurostimulation (RNS) for partial epilepsy, the optimal study design would be RCTs in which all subjects receive an RNS device, but only the treatment group has the device activated (sham control). Subjects with epilepsy may have a transient improvement in seizure frequency following any kind of neurosurgical intervention. Because RNS is considered for patients who have been refractory to other treatments, the appropriate comparison group could consist of other treatments for partial epilepsy considered to be efficacious, including medical management, surgical management, other types of implanted stimulators (e.g., vagal nerve stimulators), or a combination. Studies that compare seizure rates and seizure-free status pre- and post-RNS treatment may also provide some evidence about the efficacy of the RNS device, particularly in patients who have seizures that are refractory to multiple other treatments, in whom the natural history of seizures include persistence of seizures.

The available literature for RNS for partial epilepsy consists of 1 industry-sponsored RCT, which was used for the device’s U.S. Food and Drug Administration (FDA) approval, and multiple case series and case reports.

**Efficacy of the RNS System in the Treatment of Partial Epilepsy**

**RCTs.** RNS for epilepsy has been evaluated in 1 RCT, the RNS System Pivotal Trial, a multicenter, double-blinded, sham-controlled trial, which was the basis of FDA’s approval of the device and was published by Morrell et al in 2011.12 In this study, 191 patients with medically intractable epilepsy were implanted with the RNS device and randomized to treatment or sham control after a 1-month postimplant period in which no subjects had the device activated. Eligible patients were adults with partial-onset seizures that had not been controlled, with at least 2 trials of antiepileptic drugs (AEDs), who had at least 3 disabling seizures (motor partial seizures, complex partial 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. Ninety-seven subjects were randomized to active stimulation, and 94 to sham stimulation. After the 4-week postoperative period, patients received either sham or active stimulation according to their group. There was a 4-week stimulation optimization period, followed by a 3-month blinded evaluation period. In the evaluation period, all outcome data were gathered by a physician blinded to group assignment, and the neurostimulator was managed by a nonblinded physician. After the 3-month blinded evaluation period, all patients received active stimulation during an open-label follow-up period.
During the first postimplant month, before randomization, all subjects demonstrated a significant improvement in seizure frequency compared with baseline. 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. The mean percentage reduction in seizures was 25% in the treatment group and 20% in the sham group. (Note: these data are displayed in chart format in the Morrell et al article; mean values are taken from FDA's Summary of Safety and Effectiveness Data [SSED]).

The study'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). Seizure frequency was modeled using generalized estimating equations. The mean seizure frequency was significantly reduced in the treatment group compared with the sham group (p=0.012). FDA's SSED report provides data on the postimplant seizure frequency: during the blinded evaluation period, the mean seizure frequency in the treatment group was 22.4 (range, 0.0-226.8) (compared with a mean preimplant seizure frequency of 33.5, range 3-295); in the sham group, during the blinded evaluation period, the mean seizure frequency was 29.8 (range 0.3-44.46) (vs mean preimplant seizure frequency of 34.9; range, 3-338). During the blinded evaluation period, the treatment group experienced a -37.9% change in seizure frequency (95% confidence interval [CI], -46.7 to -27.7), while the control 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), although the absolute number of seizure-free days at baseline and follow-up is not reported. For several other secondary end points, there were no significant differences between the treatment and sham groups over the blinded evaluation period. These secondary end points included the responder rate (proportion of subjects who experienced a 50% or greater reduction in mean disabling seizure frequency compared with the preimplant period); the change in average frequency of disabling seizures for the treatment group compared with the sham group; and the change in seizure severity for the treatment group compared with the sham group.

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

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

In a follow-up to the RNS System Pivotal Trial, Heck et al compared outcomes at 1- and 2-years postimplant with baseline for patients in both groups (sham and control) who had the RNS stimulation device implanted in the RNS System Pivotal Trial.\(^1\) Of the 191 subjects implanted, 182 subjects completed follow-up to at least 1 year postimplant, and 175 subjects completed follow-up to 2 years postimplant. Six patients withdrew from the study, 4 underwent device explantation due to infection, and 5 died, with 1 death due to sudden unexplained death in epilepsy. During the open-label period, at 2 years of follow up, the median percent reduction in seizures was 53% compared with the preimplant baseline (p<0.000), and the responder rate was 55%.

AEDs could be changed during the open-label period of the trial. At the most recent follow-up, among patients with no change in AEDs, seizure reduction was 54% in patients with no change in AEDs; 61% in patients who added or increased the dose of an AED; 61% in those who discontinued or decreased an AED; and 45% in those who both increased and decreased any AED.

**Noncomparative Studies**

Before and during the pivotal RCT to evaluate the RNS system, outcomes after the use of the device were described in small case series. Anderson et al reported procedural details and clinical outcomes for 4 patients treated with the RNS device as part of the device’s pivotal clinical trial and noted that the device implant was well-tolerated and qualitatively reduced the frequency of seizures.\(^9\)

In 2004, Kossoff et al described 4 patients with intractable seizures who received neurostimulation with an external RNS (eRNS), which was a precursor to the FDA-approved implantable RNS device, during intracranial monitoring to localize seizure onset for surgery mapping.\(^8\) The eRNS is a battery-operated device that performs the same functions as the implantable RNS approved by FDA: it processes input from the implanted sensors, digitizes it, and analyzes it to determine if seizure activity is occurring, at which point it can deliver a responsive therapy consisting of a biphasic electrical pulse. For this study, the evaluation occurred during the period after patients had completed presurgical evaluation and they were awaiting removal of their intracranial electrodes. Among the 4 patients, responsive neurostimulation was noted to qualitatively reduce the frequency of seizures, and the procedure was well-tolerated.

Cases in which chronic (i.e., not responsive to detected seizure activity) focal cortical stimulation is used to treat medically refractive epilepsy have also been described.\(^13\) In these cases, cortical electrodes are placed during planned neurosurgical intervention for seizure mapping and connected to a pulse generator.

**Section Summary**

The most direct and rigorous evidence related to the effectiveness of RNS stimulation in the treatment of refractory partial seizures is from the RNS System Pivotal trial, in which patients who had partial epilepsy refractory to at least 2 medications who received RNS treatment demonstrated a significantly greater reduction in their rate of seizures compared with sham control patients. Although the single RCT available is relatively small, with 97 patients in the treatment group, all patients were treated with
the device during the open-label period (N=97 in the original treatment group and N=94 in the original sham group) and demonstrated a significant improvement in seizure rates compared with baseline. However, there were no differences in the percent of patients who responded to RNS and no difference on most of the other secondary outcomes.

Other Uses of the RNS System

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 [CURE]) that may be used by practitioners to evaluate patients’ seizures. In particular, the seizure mapping data have been used for surgical planning for patients who do not experience adequate seizure reduction with RNS placement.

DiLorenzo et al described 5 patients with refractory epilepsy who were enrolled in the RNS pivotal RCT but who did not have significant improvement in seizure activity for whom RNS output was used in the evaluation for epilepsy surgery.14 The authors report that chronic intracranial seizure monitoring allowed more accurate localization of seizure focus than in-hospital intracranial recordings, allowing sufficient confidence in a good outcome from epilepsy surgery for surgery to proceed in 4 of 5 patients.

Case series have described patients whose seizure focus has been more accurately identified with the continuous electrocorticography associated with RNS use. This is of particular relevance for patients in whom surgical resection is being considered to rule out multiple seizure foci. Spencer et al characterized the seizure localization in 6 patients with known independent bitemporal seizure foci who were enrolled in the RNS pivotal RCT to characterize the temporal and laterality patterns based on the chronic intracranial monitoring from the RNS device.15 The authors found that some patient demonstrated nonrandom spatial or temporal clustering of seizures; if this finding is replicated in other studies, it may have implications for the detection of seizure foci.

Enatsu et al reported a case in which epilepsy surgery was used in conjunction with RNS implantation to optimize therapy in a patient with mesial temporal lobe epilepsy.16 Smith et al described a patient who was enrolled in the RNS device’s pivotal trial who had previously undergone epilepsy surgery who had further improvement with the RNS device after electrocorticography revealed that his seizures were localized to an area posterior to the previously resected region.17

Safety of the RNS System

As a surgical procedure, implantation of the RNS system is associated with some 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.1

FDA’s summary of safety and effectiveness data for the RNS system summarized deaths and adverse events. 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 suicide (1 each in the pivotal and LTT studies), 1 was due to lymphoma, 1 was related to complications of status epilepticus, and 7 were attributed to possible, probable, or definite SUDEP. With 1195 patient implant years, the estimated SUDEP rate is 5.9 per 1000 implant years, which is comparable with the expected rate for patients with refractory epilepsy.11

Longer term follow-up and complication rates are not available.

### Ongoing and Unpublished Clinical Trials

An online search of ClinicalTrials.gov found on ongoing study related to the use of RNS for epilepsy.

- **RNS® System Long-term Treatment (LTT) Study (NCT00572195).** This is a nonrandomized study being conducted as a follow-up to the RNS System Feasibility and Pivotal studies, designed to evaluate the long-term safety and efficacy of the RNS system. The study is closed to enrollment, but follow-up is ongoing. The planned study enrollment is 230 subjects; the estimated study completion date is May 2018.

### Summary of Evidence

Responsive neurostimulation (RNS) for the treatment of epilepsy involves the use of 1 or more implantable electric leads that serve both a seizure detection and neurostimulation function. The device is programmed using a proprietary algorithm to recognize seizure patterns from electrocorticography output and to deliver electrical stimulation with the goal of terminating a seizure. One device, the Neuropace RNS System, has Food and Drug Administration (FDA) approval for the treatment of refractory partial epilepsy

The available literature related to the efficacy of RNS for partial epilepsy consists of 1 industry-sponsored randomized controlled trial (RCT), which was used for the device’s FDA approval, with 2-year follow up available. In addition, there were several case series and case reports. The available RCT is well-designed and reported that RNS is associated with improvements in mean seizure frequency in patients with refractory partial epilepsy, with an absolute difference in change in seizure frequency of about 20% (approximately 5 seizures per month) between groups, but that the percent of patients who responded to treatment with at least a 50% reduction in seizures was not different from sham control. The number of adverse events reported in the available studies is low. Although the data on adverse events is limited by small numbers of patients, and follow-up beyond 2 years has not been reported, patients who are candidates for RNS are generally severely debilitated, and have limited other treatment options. Therefore, RNS may be considered **medically necessary** in patients with medication-refractory partial epilepsy who are not candidates for epilepsy surgery, as outlined in the policy statement and **not medically necessary** for all other indications.

### Supplemental Information

#### Practice Guidelines and Position Statements

In 2013, a guideline on vagus nerve stimulation for the treatment of epilepsy was issued by the guideline subcommittee of the American Academy of Neurology.18 The guidelines make the following
recommendations: Vagus nerve stimulation (VNS) may be considered for seizures in children for Lennox-Gastaut syndrome (LGS) associated seizures and for improving mood in adults with epilepsy (level C); VNS may be considered to have improved efficacy over time (level C). Children should be monitored carefully for site infection after VNS implantation. More information is needed on the treatment of primary generalized epilepsy in adults. Only 1 class II article addresses this population. The effectiveness of VNS should be studied in primary generalized syndromes. The RNS system is not mentioned in this guideline.

**U.S. Preventive Services Task Force Recommendations**

Use of the RNS system is not a preventive service.

**Medicare National Coverage**

There is no national coverage determination (NCD) for the use of the RNS system in the treatment of refractory partial epilepsy.

**References**


The policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 20, 2015 and is effective April 15, 2015.

Signature on file

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