Responsive Neurostimulation for the Treatment of Refractory Partial Epilepsy

Number 7.01.143  
Effective Date July 1, 2016  
Revision Date(s) 06/14/16; 01/13/15  
Replaces N/A

Policy

Responsive neurostimulation (RNS) 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 investigational for all other indications.

Related Policies

7.01.20 Vagus Nerve Stimulation  
7.01.63 Deep Brain Stimulation

Policy Guidelines

The NeuroPace RNS® System device was approved by the FDA as an adjunctive therapy for the treatment of adults with partial seizures when:

- disabling seizures occur frequently (see Policy) and  
- the seizures do not respond to seizure medication (see Policy) and  
- less than three locations in the brain are causing the seizure activity and  
- the seizures arise from important areas of the brain that cannot be surgically removed.
Contraindications for RNS placement include:

- Three or more specific seizure foci, or
- Presence of primary generalized epilepsy, or
- Presence of a rapidly progressive neurologic disorder.

There are no specific CPT codes for the insertion of this device. It would be reported with the CPT codes for insertion of a neurostimulator as shown in the Coding table below.

<table>
<thead>
<tr>
<th>Coding</th>
<th>Description</th>
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<tbody>
<tr>
<td>61850</td>
<td>Twist drill or burr hole(s) for implantation of neurostimulator electrodes, cortical</td>
</tr>
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<td>61860</td>
<td>Craniectomy or craniotomy for implantation of neurostimulator electrodes, cerebral, cortical</td>
</tr>
<tr>
<td>61863</td>
<td>Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; first array</td>
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<td>61864</td>
<td>each additional array (List separately in addition to primary procedure)</td>
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<td>61880</td>
<td>Revision or removal of intracranial neurostimulator electrodes</td>
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<tr>
<td>61885</td>
<td>Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array</td>
</tr>
<tr>
<td>61886</td>
<td>with connection to 2 or more electrode arrays</td>
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<tr>
<td>61888</td>
<td>Revision or removal of cranial neurostimulator pulse generator or receiver</td>
</tr>
<tr>
<td>95970</td>
<td>Electronic analysis of implanted neurostimulator pulse generator system (e.g., 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 (i.e., cranial nerve, peripheral nerve, sacral nerve, neuromuscular) neurostimulator pulse generator/transmitter, without reprogramming</td>
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<td>95971</td>
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<td>Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension</td>
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<td>L8688</td>
<td>Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension</td>
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Responsive neurostimulation (RNS) for the treatment of epilepsy involves the use of 1 or more implantable electric leads that serve as 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.

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%. (2) 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. (3) 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. (4) 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. (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 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. (6) Although the mechanism of the VNS’s therapeutic effects are 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 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, 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. (7) Stimulation of the cerebellar and hippocampal regions and the subththalamic, caudate, and centromedian nuclei have also been evaluated for the treatment of epilepsy. (6)

Responsive Neurostimulation (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 preprogrammed 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. (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 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 device, 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 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. (10)

**Responsive Neurostimulation 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 [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. Several studies have described the use of the RNS in evaluating seizure foci for epilepsy surgery (11) or for identifying whether seizure foci are unilateral. (12,13)

This review does not further address use of RNS for the exclusive purposes of seizure monitoring.

**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 (14):

“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.

**Scope**

Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Benefit Application

N/A

Rationale

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<th>Populations</th>
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<th>Comparators</th>
<th>Outcomes</th>
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<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
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<td>• With refractory partial</td>
<td>• Responsive neurostimulation</td>
<td>• Vagus nerve stimulation</td>
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<tr>
<td>epilepsy</td>
<td></td>
<td>• Medical therapy</td>
<td>• Morbid events</td>
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This policy was created in November 2014 and has been updated with reviews of the literature through searches of the MEDLINE database. The most recent search was through February 9, 2016. The following is a summary of the key literature to date.

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, VNSs), or a combination. In patients with treatment-refractory epilepsy, the disease is expected to have a natural history involving persistent seizures. Therefore, studies that compare seizure rates and seizure-free status pre- and post-RNS treatment may also provide some evidence about the efficacy of the RNS device.

The body of evidence addressing whether RNS is associated with improved health outcomes for patients with partial epilepsy includes 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

**Randomized Control Trials (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.

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 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. One patient in each group did not complete the stimulus optimization period (n=1 due to subject preference in the active stimulation group; n=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 et al publication, 98 subjects had completed the open-label period and 78 had not yet completed. Eleven patients did not complete the open-label follow-up period (5 due to death, 2 to emergent explant, 4 to study withdrawal).

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]). (14).

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 (pre-implant). 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 AE 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 AE 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 AEs 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. 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.

Loring et al reported an analysis of one of the trial’s prespecified safety end points, neuropsychologic function, during the trial’s open-label period.16 Neuropsychologic testing focused on language and verbal memory, measured by the Boston Naming Test (BNT) and the Rey Auditory Verbal Learning Test (AVLT). One hundred seventy-five subjects had cognitive assessment scores at baseline and at 1 or 2 years or both and are 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 neuropsychologic outcomes were detected. On the BNT, 23.5% of subjects demonstrated RCI improvements while 6.7% had declines; on the AVLT, 6.9% of subjects demonstrated RCI improvements and 1.4% demonstrated declines.

Meador et al reported on QOL and mood outcomes for individuals in the RNS pivotal trial. (17) After the end of the blinded study period, both groups had improvements in Quality of Life in Epilepsy Inventory-89 (QOLIE-89) scores, with no statistically significant differences between groups. In analysis of those who had follow-up to 2 years post enrollment, implanted patients had statistically significant improvements in QOLIE-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.

Systematic Reviews
In 2014, Cox et al reported a systematic review of implantable neurostimulation devices, including RNS along with vagus nerve stimulation (VNS) and DBS for refractory epilepsy. (18) The evidence included on RNS in this review is primarily the pivotal RCT described previously by Morrell et al. (15) The authors concluded that RNS is “promising,” but that improvements in the accuracy of the seizure prediction method and standardization of electrical stimulation parameters are needed.

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.

The Long-Term Treatment (LTT) Study is a 7-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 et al reported 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, 3 were lost to follow-up, 28 withdrew (for reasons including pursuing other treatments [n=9], insufficient efficacy [n=5], decision to not replace RNS system after expected battery depletion [n=5] or resolution of infection [n=4], noncompliance [n=3], elective explant [n=1], and ongoing suicidality/noncompliance [n=1]), 4 underwent emergent explant, and 4 died. At years 3 and 6 of follow-up, the median percent reduction in seizures was 60% and 66%, respectively. QOL was statistically significantly improved at 4 years, with a trend toward improvement at 5 years. The most common AE was implant site infection (n=24 [9.4%]), followed by increase in complex partial seizures (n=20 [7.8%]).

Since the device’s approval, 1 single-center study reported outcomes after RNS implantation (40 surgeries) in 10 patients. (20) In this series, 1 patient had an implant site infection requiring device explantation, and a second patient had multiple lead breakages.

Earlier studies reported that the RNS implant was well-tolerated in small numbers of patients. 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)

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. (21) In these cases, cortical electrodes are placed during planned neurosurgical intervention for seizure mapping and connected to a pulse generator.
**Section Summary: Efficacy of the RNS System in the Treatment of Partial Epilepsy**

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, it was adequately powered for its primary outcome and 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. Follow-up has been reported up to 5 years postimplantation, without major increases in rates of AEs.

**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 AEs 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 AEs. 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 1,195 patient implant years, the estimated SUDEP rate is 5.9 per 1,000 implant years, which is comparable with the expected rate for patients with refractory epilepsy. (14)

Additional safety outcome have been reported out to 5 years post-implantation through the device’s LTT study (see above).

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 1.

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<th>NCT No.</th>
<th>Trial Name</th>
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<tr>
<td>NCT00572195ᵃ</td>
<td>RNS® System Post-Approval Study in Epilepsy</td>
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<td>May 2023</td>
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NCT: national clinical trial.
ᵃ Denotes industry-sponsored or cosponsored trial.

**Summary of Evidence**

The evidence for responsive neurostimulation (RNS) in individuals with refractory partial epilepsy includes 1 industry-sponsored randomized controlled trial (RCT), which was used for the device’s U.S. Food and Drug Administration approval, with several years of follow-up available, as well as case series. Relevant outcomes include symptoms, morbid events, quality of life, and treatment-related mortality and morbidity. The available RCT is well-designed and well-conducted: it 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% between groups, but noted that the percentage of patients who responded to treatment 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 by small numbers of patients, patients who are candidates for RNS are generally 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 qualitatively that the technology
results in a meaningful improvement in the net health outcome.

**Clinical Input Received from Physician Specialty Societies and Academic Medical Centers**
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 5 academic medical centers and 2 specialty medical societies (4 responses and 3 responses, respectively) when this policy was under development in 2014. There was consensus among reviewers that RNS is medically necessary for patients with partial epilepsy with 1 to 2 foci who are not candidates for resective epilepsy surgery.

**Practice Guidelines and Position Statements**

**American Academy of Neurology (AAN)**
In 2013, the guideline subcommittee of the AAN issued guidelines on vagus nerve stimulation for the treatment of epilepsy. (22) 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**
Not applicable.

**Medicare National Coverage**
There is no national coverage determination (NCD) for the use of the RNS system in the treatment of refractory partial epilepsy. In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

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**References**


Appendix
N/A

History

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<td>06/14/16</td>
<td>Annual Review. Policy updated with literature review through February 9, 2016; references 12 and 16-20 added. Policy statements unchanged.</td>
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Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2016 Premera All Rights Reserved.