Responsive neurostimulation (RNS) is a treatment that is used for partial onset epilepsy. The goal is to disrupt unusual electrical signals in the brain that trigger seizures. A stimulator is implanted, and one or two wires are placed at the location in the brain where seizures start. When the unit detects patterns that could lead to a seizure, it sends electrical signals to interrupt a seizure before it begins. RNS may be an option when medications aren't able to control symptoms. This policy describes when RNS may be considered medically necessary.

**Note:** The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
Medical Necessity

**Procedure**

**Medical Necessity**

neurostimulation (RNS) is 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 had an average of 3 or more disabling seizures (eg, 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 (eg, have an epileptic focus near eloquent cerebral cortex; have bilateral temporal epilepsy)
- Do not have contraindications for RNS placement:
  - Three or more specific seizure foci
  - Presence of primary generalized epilepsy
  - Presence of a rapidly progressive neurologic disorder.

Responsive neurostimulation (RNS) is considered investigational for all other indications not listed above.

**Coding**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>CPT</td>
<td></td>
</tr>
<tr>
<td>61850</td>
<td>Twist drill or burr hole(s) for implantation of neurostimulator electrodes, cortical</td>
</tr>
<tr>
<td>61860</td>
<td>Craniectomy or craniotomy for implantation of neurostimulator electrodes, cerebral, cortical</td>
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<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</td>
</tr>
<tr>
<td>Code</td>
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<tr>
<td>61864</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; each additional array (List separately in addition to primary procedure)</td>
</tr>
<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>Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to 2 or more electrode arrays</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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<tr>
<td>95971</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 spinal cord, or peripheral (i.e., peripheral nerve, sacral nerve, neuromuscular) neurostimulator pulse generator/transmitter, with intraoperative or subsequent programming</td>
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**HCPCS**

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<td>L8680</td>
<td>Implantable neurostimulator electrode, each</td>
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<tr>
<td>L8686</td>
<td>Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension</td>
</tr>
<tr>
<td>L8688</td>
<td>Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension</td>
</tr>
</tbody>
</table>

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**Related Information**

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
• The seizures do not respond to seizure medication
• Less than three locations in the brain are causing the seizure activity
• The seizures arise from important areas of the brain that cannot be surgically removed

Evidence Review

Description

Responsive neurostimulation (RNS) for the treatment of epilepsy involves the use of 1 or more implantable electric leads that have 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 (focal) epilepsy.

Background

Seizures and Seizure Disorders

Focal-onset 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. (A note on terminology: “focal-onset seizures” may be referred to in some studies as “partial seizures.” A 2017 position paper from the International League Against Epilepsy 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. Because most of the literature related to responsive neurostimulation uses the older classifications, we use the older terminology through much of the review.)

Focal-onset seizures were further grouped into simple partial seizures, which may be associated with motor, sensory, or autonomic symptoms, or complex partial seizures, in which 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. Of those with partial seizures, 30% to 40% have intractable epilepsy, defined as a failure to control seizures after 2 seizure medications have been appropriately chosen and used.

Epilepsy Treatment

Medical Therapy for Seizures

Standard therapy for seizures, including partial seizures, includes treatment with 1 or more antiepileptic drugs (AEDs), which include newer AEDs, like oxcarbazepine, lamotrigine, topiramate, gabapentin, pregabalin, levetiracetam, tiagabine, and zonisamide. Currently, response to AEDs is less than ideal. One systematic review comparing newer AEDs for refractory partial epilepsy reported an overall average responder rate of 34.8% in treatment groups. 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, 1 randomized controlled trial (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 freedom from seizure rates of 52%, with 28% of seizure-free individuals able to discontinue AEDs. 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. 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. 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. It has been most widely used in the treatment of Parkinson disease and other movement disorders, but it 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 the 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.

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. 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.
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 the 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 the device is implanted, 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 an 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.\textsuperscript{11}

\textbf{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\textsuperscript{12} or for identifying whether seizure foci are unilateral.\textsuperscript{13,14}

This policy does not further address use of RNS for the exclusive purposes of seizure monitoring.
Summary of Evidence

For individuals who have refractory partial (focal) epilepsy who receive responsive neurostimulation (RNS), the evidence includes 1 industry-sponsored randomized controlled trial (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 partial 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 debilitating 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 a meaningful improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

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

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
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<tr>
<td>NCT00572195</td>
<td>RNS® System Long-term Treatment (LTT) Clinical Investigation</td>
<td>230</td>
<td>May 2018</td>
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<tr>
<td>NCT02403843</td>
<td>RNS® System Post-Approval Study in Epilepsy</td>
<td>375</td>
<td>May 2023</td>
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NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.
Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may provide appropriate reviewers who collaborate with and make recommendations during this process, 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 2 specialty medical societies (3 responses) and 5 academic medical centers (4 responses) when this policy was under development in 2014. There was consensus among reviewers that responsive neurostimulation is medically necessary for patients with partial epilepsy with 1 to 2 foci who are not candidates for resective epilepsy surgery.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

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:

“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.
References


### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/13/15</td>
<td>New Policy. Policy created with literature review through June 30, 2014 and review of clinical input. Responsive neurostimulation may be considered medically necessary for refractory partial epilepsy when criteria are met. Reformatted the policy guidelines for improved clarification.</td>
</tr>
<tr>
<td>07/01/16</td>
<td>Annual Review, approved on June 14, 2016. Policy updated with literature review through February 9, 2016; references 12 and 16-20 added. Policy statements unchanged.</td>
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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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