Responsive Neurostimulation for the Treatment of Refractory Focal Epilepsy

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DESCRIPTION

Responsive neurostimulation (RNS) consists of a cranially implanted, programmable cortical neurostimulator for the treatment of focal epilepsy that involves the use of 1 or more implantable electrode leads that serve as both a seizure detection and neurostimulation function. The device provides what the manufacturer refers to as “responsive cortical stimulation.” The device is programmed using a proprietary algorithm to recognize seizure patterns from electrocorticography output (an electroencephalogram made with electrodes that are in direct contact with the brain) and to deliver electrical stimulation with the goal of terminating a seizure before onset.
Neurostimulation devices are classified as one of two types: chronic programmed stimulation devices that administer stimulation at regular preprogrammed intervals (continuous or intermittent) and responsive neurostimulation (RNS) devices that deliver stimulation directly to the brain at the seizure focus only in response to device-detected, abnormal electrical brain activity. The chronic programmed stimulation methods available for treating epilepsy include vagus nerve stimulation (VNS). Responsive neurostimulation is intended to reduce seizures in patients diagnosed with partial (focal) onset of seizures that are refractory to medical therapy and are not candidates for surgical resection.

There are two broad categories of seizures: focal and generalized. Focal seizures (previously referred to as partial seizures) involve only one area of the brain, typically part of one lobe of one hemisphere. A focal seizure can be associated with impairment of consciousness or awareness (previously called complex partial seizure) or no impairment of consciousness (previously called simple partial seizures).

- **Focal seizures without loss of consciousness**: Once called simple partial seizures, these seizures do not cause loss of consciousness. They may alter emotions or change the way things look, smell, feel, taste or sound. They may also result in involuntary jerking of a body part, such as an arm or leg, and spontaneous sensory symptoms such as tingling, dizziness, and flashing lights.

- **Focal seizures with impaired awareness**: Once called complex partial seizures, these seizures involve a change or loss of consciousness or awareness. During a complex partial seizure, an individual may stare into space and not respond normally to their environment or perform repetitive movements, such as hand rubbing, chewing, swallowing or walking in circles.

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 2 seizure medications have been appropriately chosen and used.

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. Currently, response to AEDs is less than ideal: 1 systematic review comparing newer AEDs for refractory focal epilepsy reported an overall average responder rate in treatment groups of 34.8%. As a result, a substantial number of patients do not achieve good seizure control with medications alone.

When a seizure focus can be identified, seizure control may be achieved through surgical resection or transection of the seizure focus, which is considered to be the most effective therapy; however, some patients are not candidates for this type of surgery. Patients may
not be candidates for 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. Treatment options are very limited for patients with medically refractory epilepsy who are not candidates for surgical resection. These patients may pursue alternative treatments which includes neurostimulation.

Responsive neurostimulation (RNS) shares some features with deep brain stimulation (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.

The development of RNS system arose from observations related to the effects of cortical electrical stimulation for seizure location. It has been observed that electrical cortical stimulation can terminate induced and spontaneous electrographic seizure activity. 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 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.

Clinical Context and Purpose
The purpose of responsive neurostimulation in individuals with refractory focal epilepsy to provide a treatment option to or an improvement on existing therapies.

Patients
The relevant population of interest is individuals with refractory focal epilepsy. Focal seizures (previously referred to as partial seizures) arise from a discrete area of the brain and can cause a range of symptoms, depending on the seizure type and the brain area involved. Focal seizures are further grouped into simple focal seizures, which may be associated with motor, sensory, or autonomic symptoms, or complex focal seizures, in which consciousness is affected. Complex focal seizures may be associated with abnormal movements (automatisms). In some cases, focal seizures may result in secondary generalization, in which widespread brain electrical activity occurs after the onset of a focal seizure, thereby resulting in a generalized seizure.

Interventions
The therapy being considered is responsive neurostimulation.
One device, the Neuropace RNS System, is currently approved by the FDA and is commercially available in the United States. The system consists of the implant and external components. The implant is the RNS neurostimulator (generator) and leads (tiny wires containing electrodes connected to the target areas of the brain). The neurostimulator is a battery powered microprocessor-controlled generator that is placed within the skull and beneath the scalp. It connects to one or two leads inserted into the brain (depth lead) and on the brain surface in the area of the seizure focus (cortical strip lead). Both the depth lead(s) and the cortical strip lead(s) can detect the electrical activity of the brain and deliver stimulation. The external components include the programmer, remote monitor, telemetry wand and a patient data management system. The programmer provides the clinician with a user interface to select and download operating parameters to the RNS neurostimulator for detection and responsive stimulation settings, to view real time ECoG signals, to test the RNS system integrity, and to upload data and diagnostic information from the neurostimulator for review. The remote monitor is a home use monitoring device used to collect data from the RNS neurostimulator and upload the data using telephone lines to the internet by way of a secure connection to the PDMS (patient data management system). The uploaded data are accessible for review by clinicians by way of a secure connection to the PDMS. This offers a convenient option for remotely monitoring the RNS neurostimulator between patient visits to the clinic. The patient data management system (PDMS) is a secure website that provides a means for a clinician to review information that has been transmitted by the programmer and remote monitor.

Before device implantation, the patient undergoes seizure localization, which includes video-EEG monitoring and magnetic resonance imaging for detection of epileptogenic lesions. Additional testing may also include EEG with intracranial electrodes, intraoperative or extra operative 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 on the cortical surface, while the depth leads are recommended for seizure foci beneath the cortical surface. The neurosurgeon performs a scalp incision and then drills two to four burr holes in the skull to allow for lead placement. The surgeon typically implants the depth leads using specialized localization tools and planning software and implants the cortical strip leads on the brain surface under the dura. After securing the leads the surgeon removes the area of skull that conforms precisely to the neurostimulator (craniotomy) to accommodate the neurostimulator. The neurostimulator rests in a frame above the dura and does not touch the brain. After connecting the leads to the neurostimulator, the surgeon programs the neurostimulator for initial use 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.

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Comparators
Because RNS is considered for patients refractory to other treatments, the appropriate comparison group could consist of other treatments for focal epilepsy considered to be efficacious, including medical management, surgical management, other types of implanted stimulators (eg, vagal nerve stimulators), 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 evidence about the efficacy of the RNS device.

Outcomes
The general outcomes of interest are symptoms, morbid events, quality of life and treatment related mortality and morbidity.

RNS for Treatment of Refractory Focal Epilepsy
The RNS system was approved on the basis of data from three trials: an initial Feasibility study, the Pivotal Trial and a Long Term Treatment Investigation trial (LTT).

The Feasibility study was a multi-center clinical investigation of individuals with medically intractable epilepsy. Sixty-five subjects were implanted with the RNS neurostimulator and leads in the feasibility study. Eligible subjects were 18-65 years of age with medically intractable partial onset seizures and a minimum of 4 simple partial seizures (motor or sensory), complex partial seizures, and/or secondarily generalized seizures in each of the previous three months. Subjects were required to be on a stable antiepileptic medication regimen and must have previously undergone diagnostic testing and localized one or two epileptogenic region(s). Subjects with psychogenic or non-epileptic seizures, status epilepticus, active psychosis, severe depression, or suicidal ideation within the preceding year were excluded. The first four subjects implanted with the RNS neurostimulator and leads at a clinical site participated in an open label protocol (all subjects received responsive neurostimulation), and subsequent subjects at that site participated in a randomized, double-blind, concurrent sham-stimulation control protocol in which the treatment group received stimulation and sham group did not. Forty-two subjects were in the open label protocol and 23 were in the blinded protocol. Following completion of the 16 week evaluation period, subjects transitioned to an open label period, and all subjects were able to receive responsive stimulation. Subjects continued in the open label period through the end of the study participation, which was 2 years post implantation. The Feasibility study was designed to evaluate preliminary safety and effectiveness. The results were used to inform the design of the Pivotal Study and to assess the integrity of the blind.

The Pivotal Trial results were reported by Morrell (2011). This study involved the use of the RNS system in a randomized, double-blinded, multi-center, sham-controlled clinical investigation that initially enrolled 240 subjects. A total of 49 subjects were excluded prior to implantation, leaving 191 subjects for analysis. Eligible subjects were 18-70
years of age, partial onset seizures refractory to at least two trials of anti-epileptic drugs, had experienced at least three disabling seizures per month and had either one or two epileptogenic region(s) localized. All subjects underwent implantation of the RNS system followed by one month break-in period followed by randomization. Subjects were assigned to either active or sham therapy, and followed for the 12 week blinded treatment phase, then an 84 week open-label period where all subjects received active therapy. The authors reported that the blind was successfully maintained (blinding index 0.5727). Both groups experienced a reduction in mean seizure frequency during the first post-implant month prior to randomization. However, this reduction abated during the blinded period in the sham group until, in the final month of the blinded period, seizure frequency approached pre-implant levels. Mean seizure frequency was significantly reduced in the treatment group vs. the sham group (p=0.012) during the blinded period. The responder rate (percentage of subjects with a ≥ 50% reduction in seizures) over the blinded period was not significant overall, with 29% in the treatment group responding versus 27% in the sham group. However, seizure free day over the first month continued to increase in the treatment group but declined for the sham group. By the third month, the treatment group had 27% fewer days with seizures versus 16% fewer days in the sham group (p=0.048). During the open-label period, the sham group demonstrated a statistically significant reduction in mean seizure frequency compared to the pre-implant period (p=0.04). Across all subjects, the reduction was sustained, and even improved, over time. The responder rate at one year post-implant was 43% (n=177) and 46% (n=102) at 2 years. As of the data cutoff date, 13 subjects (7.1%) were seizure free over the most recent 3 month period. The Quality of Life in Epilepsy-89 (QOLIE-89) assessment tool overall t-scores were significantly improved in both groups at the end of the blinded period (p=0.040), 1 year (p=0.001) and 2 years (p=0.016). During the blinded period, there was no difference between the treatment and sham groups in the frequency of cognitive adverse events, or any neuropsychological measure through 2 years. No adverse changes in mood inventories were reported at any time point in the study. The serious adverse event rate for medical and surgical events for the first 84 weeks was 18.3%. This compares favorably to comparator rates for deep brain stimulation (DBS). There was no difference between the treatment and sham groups in the percentage of subjects with mild or serious adverse events over the blinded period, and included intracranial hemorrhage due to surgical complications and subdural hematomas attributed to seizure-related head trauma. Six subjects died, but not were attributed to responsive cortical stimulation treatment. The authors concluded, improvements in QOL (quality of life) overall and in domains related to health concerns, social functioning, and cognition support the clinical meaningfulness of the treatment response. Safety was acceptable compared to alternative and comparable procedures and to the risks of frequent seizures. Stimulation was well tolerated and there were no adverse effects on cognition or mood. Given these findings, responsive cortical stimulation may provide another much-needed treatment option for persons with medically intractable partial seizures.

The final part of the FDA submission data came from the Long-Term Treatment Study (LTT) is an ongoing open-label multi-center prospective clinical study of those subjects who completed the Feasibility trial (57 subjects) and the Pivotal Trial (173 subjects), for
a total of 230 subjects. During the LTT study, subjects can continue to receive responsive stimulation. Each subject participates for a maximum of 7 years. Adverse event and seizure data are collected at 6 month intervals, and data regarding quality of life are collected at yearly intervals. Antiepileptic drug adjustments are permitted as needed.

The first published report data from the Long-Term Treatment Study (LTT) was made available in 2015 (Bergey 2015). This report included data from 191 subjects who have completed data at the 6 year cutoff point, but data are presented based on the entire subject pool. The median reduction seizures was 60% at 3 years and 66% at 6 years. The responder rates at the same time points were 58% and 59%. Adjusted response rates taking into account withdrawals at the same time points were 58% and 56%. Based on data from the last 3 months of the collection period, 84% of subjects had some improvement, 60% had 50% or greater reduction in seizure frequency, and 16% were seizure free. Only 8% had a 50% or greater increase in seizure activity. Over one-third of subjects experienced a 3 month seizure free interval, and 23% experienced one of 6 months or longer. QOLIE-89 measures through year 5 continued to improve significantly (p<0.001). Serious events were reported in 2.5% or more of the subject at any time during the study period. Three intracranial hemorrhages were reported at 18 months, 2.5 years and 2.8 years following device implantation. Death was reported for 11 subjects, including 2 suicides, 1 status epilepticus, 1 lymphoma and 7 possible SUDEP (sudden unexpected death in epilepsy). The device was off at the time of 2 SUDEP deaths. The authors concluded these results are promising, and demonstrate continued significant benefit to the use of the RNS system in subjects with epilepsy.

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.

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 7 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 refractory epilepsy.

Additional safety outcomes have been reported to 5 years post-implantation through the device’s long-term treatment (LTT) study (see above).
As of March 13, 2019, there were 203 reports in the FDA Manufacturer and User Facility Device Experience database for product code PFN. Five were labeled as event type “Malfunction,” one was extended hospitalization due to aphasia, and all remaining reports were labeled as “Injury.” Seven of the “Injury” event narratives mentioned hemorrhages, 3 stroke, 6 fluid leakage, 46 infection, 5 swelling or edema, and in 5 the device had become exposed.

**Summary of Evidence**
For adult individuals who have refractory focal epilepsy who receive responsive neurostimulation (RNS), the evidence includes an industry sponsored randomized controlled trial (RCT), which was used for Food and Drug Administration (FDA) approval of the NeuroPace RNS system. The Pivotal Trial was well-designed and well conducted; it reported that RNS is associated with improvements in mean 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 available studies is low. Generally, patients who are candidates for responsive neurostimulation (RNS) are severely debilitated and have few other treatment options, so the benefits are likely high relative to risk. In particular, patients who are not candidates for respective surgical resection (epilepsy surgery) and have few treatment options may benefit from RNS. The evidence is sufficient to determine that technology results in a meaningful improvement in the net health outcome in adult patients.

In 2019, ECRI executive summary regarding the RNS System (NeuroPace, Inc) for treating pediatric epilepsy stated the following: Evidence is inconclusive; Clinical studies show the RNS system can effectively control partial-onset epileptic seizures in adults with medically refractory epilepsy; however, these findings may not generalize to children and adolescents because of differences in brain physiology and disease etiology. Evidence of RNS safety and effectiveness in pediatric patients is limited to case reports of three patients and does not permit conclusions. No clinical studies of RNS treatment in pediatric patients are ongoing; however, ECRI searches identified numerous U.S. children's hospitals offering RNS off-label for children with medically refractory focal epilepsy. The evidence is insufficient to determine the technology results in meaningful improvement in net health outcomes.

**Practice Guideline and Position Statements**
There were no practice guideline or position statements identified.

**Regulatory Status**
November 2013, the NeuroPace RNS system (Neuropace Inc., Mountain View, CA) was approved by the 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 secondary 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 will less frequent seizures.”

**PRIOR APPROVAL**

Not applicable.

**POLICY**

*See also medical policy*

- 07.01.60 Vagus Nerve Stimulation (VNS) and Vagal Blocking Therapy

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

- Are 18 years or older; **and**
- Have a diagnosis of focal seizures with 1 or 2 well localized seizure foci identified; **and**
- Have an average of 3 or more disabling seizures (e.g., motor focal seizures, complex focal seizures, or secondary generalized seizures) per month over the prior 3 months; **and**
- Are refractory to medical therapy (have failed 2 or more appropriate antiepileptic medications at therapeutic doses); **and**
- Are not candidates for focal respective epilepsy surgery (e.g., have an epileptic focus near eloquent cerebral cortex, have bilateral temporal epilepsy); **and**
- Do not have contraindications for RNS placement (contraindications for RNS placement include: 3 or more specific seizure foci; or presence of primary generalized epilepsy; or presence of a rapidly progressive neurologic disorder).

A replacement or revision of a responsive neurostimulation (RNS) (generator, leads and/or battery) may be considered **medically necessary** for an individual who meets **ALL** of the above criteria, and the existing device is no longer under warranty and cannot be repaired.

Responsive neurostimulation (RNS) is considered **investigational** for all other indications to include when the above criteria are not met as there is insufficient evidence to support the safety and effectiveness concerning net health outcomes.
PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 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 (e.g. 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
- 95970 Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g. contact group(s), interleaving, amplitude, pulse width, frequency [Hz], on/off cycle, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve neurostimulator pulse generator/transmitter without programming
- 95971 Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group(s), interleaving, amplitude, pulse width, frequency [Hz], on/off cycling burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithm, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with simple spinal cord or peripheral nerve (e.g. sacral nerve) neurostimulator pulse generator/transmitter programming by physician or other qualified care professional
- 95983 Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group(s), interleaving, amplitude, pulse width, frequency [Hz], on/off
- 95984 Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group(s), interleaving, amplitude, pulse width, frequency [Hz], on/off

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cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain neurostimulator pulse generator/transmitter programming, each additional 15 minutes face-to-face time with physician or other qualified health care professional (List separately in addition to code for primary procedure)

- C1767 Generator neurostimulator (implantable) non-rechargeable
- C1778 Lead, neurostimulator (implantable)
- C1787 Patient programmer, neurostimulator
- C1816 Receiver and/or transmitter, neurostimulator (implantable)
- C1820 Generator, neurostimulator (implantable), non high frequency with rechargeable battery and charging system
- C1822 Generator, neurostimulator (implantable), high frequency with rechargeable battery and charging system
- C1897 Lead, neurostimulator test kit (implantable)
- L8679 Implantable neurostimulator, pulse generator any type
- L8680 Implantable neurostimulator electrode, each
- L8681 Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only
- L8682 Implantable neurostimulator radiofrequency receiver
- L8683 Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
- L8685 Implantable neurostimulator pulse generator, single array, rechargeable includes extension
- L8686 Implantable neurostimulator pulse generator, single array, nonrechargeable, includes extension
- L8687 Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
- L8688 Implantable neurostimulator pulse generator, dual array, nonrechargeable, includes extension
- L8689 External recharging system for battery (internal) for use with implantable neurostimulator, replacement only

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### POLICY HISTORY

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New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

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