BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:
Responsive Neurostimulation for the Treatment of Refractory Focal Epilepsy

Policy #: 574 | Latest Review Date: May 2019
Category: Surgery | Policy Grade: B

Background:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

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Description of Procedure or Service:

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 focal (formerly partial) epilepsy.

Seizures and Seizure Disorders

Focal seizures (previously referred to as 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.

Focal seizures may be further grouped into simple focal seizures, which may be associated with motor, sensory, or autonomic symptoms, or complex focal seizures, in which patients' 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.

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 focal seizures. Thirty percent to 40% of those with focal seizures have intractable epilepsy, defined as a failure to control seizures after 2 seizure medications that have been appropriately chosen and used.

Epilepsy Treatment

Medical Therapy for Seizures

Standard therapy for seizures, including focal seizures, includes treatment with one 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. However, response to AEDs is less than ideal: One systematic review of comparisons between multiple newer AEDs for refractory focal 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, one 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 focal seizures) is associated with five-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 in the brain has been used as therapy for epilepsy, either as an adjunct to or as an alternative to medical or surgical therapy. Vagus nerve stimulation (VNS) has been widely used for refractory epilepsy, following 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 1RCT, 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.

Responsive Neurostimulation 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.

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 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 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.

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 or for identifying whether seizure foci are unilateral.

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

Policy:

Effective for dates of service on or after November 1, 2014:

Blue Advantage will treat **responsive neurostimulation** as a **covered benefit** for patients with focal epilepsy who meet **ALL** of the following criteria:

- Are 18 years or older.
- Have a diagnosis of focal seizures with 1 or 2 well-localized seizure foci identified.
- 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;
- 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. *

Blue Advantage will treat **responsive neurostimulation** as a **non-covered benefit** and as **investigational** for all other indications.

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

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The most recent literature review was updated through February 5, 2019.

The clinical evidence to determine whether the use of technology improves the net health outcome is assessed by evidence reviews. Health outcomes are assessed by the length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Outcome measures are validated to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

The net health outcome of technology is assessed by whether the evidence is sufficient enough to draw conclusions, while examining two domains: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. In various conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence is determined by study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is favored to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

For the evaluation of responsive neurostimulation (RNS) for focal 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 focal 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.

The body of evidence addressing whether RNS is associated with improved health outcomes for patients with focal 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.

RNS for Treatment of Refractive Focal Epilepsy

Clinical Context and Test Purpose

The purpose of responsive neurostimulation in individuals with refractory focal epilepsy is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: In patients with refractory focal epilepsy, does responsive neurostimulation therapy improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

Patients

The patient 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 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-electroencephalographic monitoring and magnetic resonance imaging for detection of epileptogenic lesions. Additional testing may include electroencephalography 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.

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 (e.g., 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
Symptoms, morbid events, quality of life, and treatment-related mortality and morbidity are the outcomes of interest.

RNS for Treatment of Refractory Focal Epilepsy
The body of evidence addressing whether RNS is associated with improved health outcomes for patients with focal epilepsy includes an industry-sponsored RCT, which was used for the device's U.S. Food and Drug Administration (FDA) approval, as well as multiple case series and case reports.

Pivotal Trial
RNS for epilepsy has been evaluated in the RNS System Pivotal Trial, and 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. In this study, 191 patients with medically intractable focal epilepsy were implanted with the RNS device and randomized to treatment or sham control after a one-month post implant period in which no subjects had the device activated. Eligible patients were adults with focal seizures that had not been controlled, with at least two trials of antiepileptic drugs (AEDs), who had at least three disabling seizures (motor focal seizures, complex focal seizures, or secondary generalized seizures) per month on average, and who had standard diagnostic testing that localized one or two epileptogenic foci. Thirty-two percent of those implanted had prior epilepsy surgery, and 34% had a prior vagal nerve stimulator.

Ninety-seven subjects were randomized to active stimulation, and 94 to sham stimulation. After the four-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 three-month blinded evaluation period. In the evaluation period, all outcome data were gathered by a physician blinded to group assignment, and the neurostimulator was managed by a non-blinded 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 three-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 (n=5, n=2, and n=4 due to death, emergent explant, and study withdrawal, respectively).

The trial's primary effectiveness objective was to demonstrate a significantly greater reduction in the frequency of total disabling seizures in the treatment group compared with the sham group during the blinded evaluation period relative to baseline (pre-implant). The mean pre-implant 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 trial's primary effectiveness objective was to demonstrate a significantly greater reduction in the frequency of total disabling seizures in the treatment group compared with the sham group during the blinded evaluation period relative to baseline (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 post implant seizure frequency: during the blinded evaluation period, the mean seizure frequency in the treatment group was 22.4 (range, 0.0-226.8) and (compared with a mean pre-implant 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 pre-implant seizure frequency of 34.9; range, 3-338). 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 pre-implant period); the change in average frequency of disabling seizures or change in seizure severity.

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

Follow-Up Analyses to the Pivotal Trial Subjects

In a follow-up to the RNS System Pivotal Trial, Heck et al (2014) compared outcomes at one- and two-years post implant 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 one year post implant, and 175 subjects completed follow-up to 2 years post implant. 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 pre-implant baseline ($p<0.000$), and the responder rate was 55%.

Loring et al (2015) reported an analysis of one of the trial's prespecified safety endpoints, neuropsychological function during the trial's open-label period. Neuropsychologic testing focused on language and verbal memory, measured by the Boson 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, there were no significant group-level declines in any neuropsychological outcomes detected. On the BNT, 23.5% of subjects demonstrated improvements while 6.7% had declines; on the AVLT, 6.9% of subjects demonstrated improvements and 1.4% demonstrated declines.

Meador et al (2015) reported on QOL and mood outcomes for individuals in the RNS pivotal trial. 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 (BDI) and the Profile of Mood States (POMS), 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 deep brain stimulation (DBS) for refractory epilepsy. The evidence included on RNS in this review is primarily the pivotal RCT described previously (Morrell et al). The authors conclude that RNS is "promising," but that improvements in the accuracy of the seizure prediction method and standardization of electrical stimulation parameters are needed.

Gooneratne et al (2016) performed a systematic review comparing neurostimulation technologies in refractory focal epilepsy. They performed a literature search for studies with long-term efficacy data (≥5 years) and at least 30 patients evaluating VNS, cortical responsive stimulation, or DBS in refractory focal epilepsy using PubMed and Cochrane databases in November 2015.

No direct comparisons of the technologies were found. The previously described pivotal trial of RNS was the only RNS study included. Indirect comparisons of the technologies were limited by differences in RCT inclusion criteria, definition of response and methods of data collection between studies. Reviewers concluded that all 3 neurostimulation technologies showed long-term efficacy, with progressively better seizure control over time.

Noncomparative Studies

Before and during conduct of 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 LTT Study participants (of a total of 230 originally enrolled in the LTT Study) for a median 5.4 years. Of those who discontinued the study, 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 year 3 and year 6, 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 adverse event 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. 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. In 2004, Kossoff et al reported qualitative reduction in seizure frequency in 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.

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. In these cases, cortical electrodes are placed during planned neurosurgical intervention for seizure mapping and connected to a pulse generator.

Section Summary: RNS for Treatment of Refractory Focal Epilepsy

The most direct and rigorous evidence related to the effectiveness of RNS stimulation in the treatment of refractory focal seizures is from the RNS System Pivotal trial, in which patients who had focal epilepsy refractory to at least two medications 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 post implantation, without major increases in rates of adverse events.

Adverse Events 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.

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 (one each in the pivotal and LTT studies), one was due to lymphoma and another related to complications of status epilepticus, and seven 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 refectory epilepsy.

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

As of March 13, 2019, there were 203 reports in the FDA Manufacturer and User Facility Device Experience (MAUDE) 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 strokes, 6 fluid leakages, 46 infections, 5 swelling or edema, and in 5 the device had become exposed.

Summary of Evidence
For individuals who have refractory focal epilepsy who receive responsive neurostimulation (RNS), the evidence includes one 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 focal epilepsy, with an absolute difference in change in seizure frequency of about 20% between groups, though the percentage of treatment responders with at least a 50% reduction in seizures did not differ from sham control. Overall, the results suggested a modest reduction in seizure frequency in a subset of patients. The number of adverse events reported in the available studies is low, although the data on adverse events were limited because small study samples. Generally, patients who are candidates for RNS are severely debilitated and have

few other treatment options, so the benefits are likely high relative to the risks. In particular, patients who are not candidates for respective 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.

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. The guidelines make the following recommendations: Vagus nerve stimulation (VNS) may be considered for seizures in children for Lennox-Gastaut syndrome–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 RNS system is not mentioned in this guideline.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Key Words:
RNS System, NeuroPace®, epilepsy, partial seizures, responsive neurostimulation, electrocorticography, chronic unlimited cortical electrocorticography, CURE

Approved by Governing Bodies:
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 two epileptogenic foci, are refractory to 2 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 2 seizures), and has not been evaluated in patients with less frequent seizures."

Benefit Application:
Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

Current Coding:

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 such as the following:

CPT 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

95836 Electrocorticogram from an implanted brain neurostimulator pulse generator/transmitter, including recording, with interpretation and written report, up to 30 days **(Effective 01/01/2019)**

95970 Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off 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, cranial nerve, spinal cord, peripheral nerve, or sacral nerve, neurostimulator pulse generator/transmitter, without programming

HCPCS Codes:

L8680 Implantable neurostimulator electrode, each

L8686 Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension

L8688 Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension

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Policy History:

Adopted for Blue Advantage, November 2014
Available for comment December 2, 2014 through January 16, 2015
Medical Policy Group, April 2016
Medical Policy Group, April 2017
Medical Policy Group, April 2018
Medical Policy Group, December 2018: 2019 CPT coding update.
Medical Policy Group, May 2019

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.