MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**Responsive Neurostimulation for the Treatment of Refractory Focal Epilepsy**
Policy Number	**7.01.103**
Category	**Technology Assessment**
Original Effective Date	**04/16/20**
Committee Approval Date	**04/16/20, 04/15/21, 04/21/22**
Current Effective Date	**04/18/24**
Archived Date	**04/21/22**
Archive Review Date	**04/20/23, 04/18/24**
Product Disclaimer	• *Services are contract dependent; if a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan or Child Health Plus product), medical policy criteria apply to the benefit.* • *If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.* • *If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.* • *If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line*

POLICY STATEMENT

I. Based upon our criteria and assessment of the peer-reviewed literature, responsive neurostimulation has been medically proven to be effective and, therefore, is considered **medically appropriate** for patients with refractory focal epilepsy who meet **ALL** of the following criteria:
   A. are 18 years or older;
   B. have a diagnosis of focal seizures with one (1) or two (2) well-localized seizure foci identified;
   C. have had an average of three (3) or more disabling seizures (e.g., motor focal seizures, complex focal seizures, or secondary generalized seizures) per month over the prior three (3) months;
   D. are refractory to medical therapy (have failed two (2) or more appropriate antiepileptic medications at therapeutic doses);
   E. are not candidates for focal resective epilepsy surgery (e.g., have an epileptic focus near the eloquent cerebral cortex; have bilateral temporal epilepsy);
   F. does not have **ANY** of the following contraindications for responsive neurostimulation device placement:
      1. have three (3) or more specific seizure foci;
      2. have primary generalized epilepsy;
      3. have a rapidly progressive neurologic disorder;
      4. have one (1) or more implanted medical devices that delivers electrical energy to the brain;
      5. are unable or do not have the necessary assistance to properly operate the device or magnet; **or**
      6. are high risk for surgical complications (e.g., active systemic infection or coagulation disorders [e.g., use of antithrombotic therapies or platelet count below 50,000]).

II. Based upon our criteria and assessment of the peer-reviewed literature, responsive neurostimulation has not been medically proven to be effective and, therefore, is considered **investigational** for all other indications.

III. Repair and/or replacement of a medically necessary responsive neurostimulator and/or components not under warranty will be considered **medically appropriate** when the following criteria are met:
   A. Physician documentation includes **ALL** of the following:
      1. date of device implantation/initiation,
      2. manufacturer warranty information,
      3. attestation that the patient has been compliant with the use of device and will continue to benefit from the use of device; **AND ONE OF THE FOLLOWING APPLY:**
   B. Repair of the currently used device when **ALL** of the following are met:
      1. it is no longer functioning adequately,
      2. inadequate function interferes with activities of daily living, and
      3. repair is expected to make the equipment fully functional (as defined by manufacturer); **or**
   C. Replacement of the currently used device when the following are met:
      1. it is no longer functioning adequately, **AND EITHER:**
      2. has been determined to be non-repairable, **or**
      3. the cost of the repair is in excess of the replacement cost; **or**
   D. Replacement of the currently used device when **BOTH** of the following are met:
      1. there is documentation that a change in the patient's condition makes the present unit non-functional, **and**
      2. improvement is expected with a replacement unit.

IV. The replacement of a properly functioning responsive neurostimulator and/or external components is considered **not medically necessary**. This includes, but is not limited to, replacement desired due to advanced technology or in order to make the device more aesthetically pleasing.

V. Repair or replacement of equipment damaged due to patient neglect, theft, abuse, or when another available coverage source is an option (e.g., homeowners, rental, auto, liability insurance, etc.) is **ineligible for coverage**.

Refer to Corporate Medical Policy #7.01.05 Vagus Nerve Stimulation and Vagus Nerve Blocking Therapy

Refer to Corporate Medical Policy #7.01.23 Deep Brain Stimulation

Refer to Corporate Medical Policy #11.01.03 Experimental or Investigational Services

DESCRIPTION

Seizures have been defined as paroxysmal disorders of the central nervous system characterized by abnormal cerebral neuronal discharge with or without loss of consciousness. Medically refractory seizures are defined as seizures that occur in spite of therapeutic levels of antiepileptic drugs or seizures that cannot be treated with therapeutic levels of antiepileptic drugs because of intolerable adverse effects of these drugs.

The goal of epilepsy surgery is to either remove the seizure-producing area of the brain or to limit the spread of seizure activity. Surgical results can be considered curative (stopping the seizures) or palliative (restricting the spread of the seizure). The type of surgery performed is dependent on the type of seizure and where the seizures begin in the brain. Curative procedures (e.g., temporal lobectomy, cortical excision, hemispherectomy) are performed when tests consistently point to a specific area of the brain where the seizures begin. Palliative procedures (e.g., corpus callosotomy, subpial transections) are performed when a seizure focus cannot be determined, or there are multiple seizure foci, or the seizure onset zone overlaps brain areas critical for speech, movement, or vision.

Responsive neurostimulation (RNS, NeuroPace Inc., Mountain View, CA) is considered a palliative option in patients for whom resective surgery is not possible (e.g., two seizure foci, focus on the eloquent cortex) but whose seizure focus or foci can be identified. The NeuroPace RNS System is an implantable therapeutic device that continuously monitors brain electrical activity, detects abnormal electrical activity, and responds by delivering electrical stimulation of up to two epileptic focus areas, to normalize that activity before an individual experiences seizures. The NeuroPace RNS System includes a cranially implanted programmable neurostimulator, which is connected to one or two depth and/or subdural cortical strip leads that are surgically placed in or on the brain at the seizure focus. The implant procedure typically takes

place during one inpatient stay. Battery life is about eight years, and revision is typically a same-day procedure. The RNS Neurostimulator model RNS320 is considered magnetic resonance (MR) conditional. MR imaging may be performed safely on patient implanted with the RNS320 system only under very strict, specific conditions defined in their magnetic resonance imaging (MRI) Guidelines manual.

There are some key differences between the RNS System and other neurostimulators. Open-loop stimulations, such as deep brain stimulation (DBS), deliver scheduled intermittent stimulations for a pre-set duration and may not necessarily be applied during an ictal period. The RNS System is a closed-loop stimulator and only provides stimulation when abnormal electrical activity is detected. After the first stimulation, if seizure activity is redetected, it will deliver up to a maximum of five consecutive stimulations. The RNS System depth electrodes or subdural cortical strip leads also act as recording instruments, which continuously monitor brain electrical activity and store electrocorticograms (ECoG) for later review. This information is used by practitioners to optimize programming of the RNS System neurostimulator, to reduce seizure frequency, make informed decisions regarding the patient's progress, and diagnose any changes in the epileptiform discharges. Due to the limited number of ECoGs that can be stored on the device, patients or caregivers must be able to regularly record and download data.

RATIONALE

The U.S. Food and Drug Administration (FDA) approved the NeuroPace RNS System in 2013 (P100026) for the adjunctive treatment of medically intractable focal epilepsy in adults with frequent and disabling seizures (motor partial seizures, complex partial seizures, and/or secondarily generalized seizures), who have undergone diagnostic testing that localized no more than two epileptogenic foci and are refractory to two or more antiepileptic medications. The RNS System has demonstrated safety and effectiveness in patients who average three or more disabling seizures per month over the three most recent months (with no fewer than two seizures in any month) but has not been evaluated in patients with less frequent seizures. Patients who are not candidates for resective epilepsy surgery and have few treatment options may benefit from the RNS System. The evidence includes an industry-sponsored RCT, as well as a long-term, open-label study, and is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

The RNS System Pivotal Trial (Morrell et al., 2011) was a multicenter, double-blinded, sham-controlled trial in which 191 patients with medically intractable focal epilepsy were implanted with the RNS System device and randomized to treatment or sham control one month after device implantation. Eligible patients were adults with focal seizures whose epilepsy 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. Patients were randomized to active stimulation (n=97) or sham stimulation (n=94). After the four-week post-operative period, patients received either sham or active stimulation, according to group assignment. There was a four-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 nonblinded physician. One patient in each group did not complete the stimulus optimization period (one due to subject preference in the active stimulation group; one 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 publication, 98 subjects had completed the open-label period, and 78 had not. Eleven patients did not complete the open-label follow-up period (five due to death, two to emergent explant, four to study withdrawal). 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. Mean seizure frequency modeled using generalized estimating equations was significantly reduced in the treatment group, compared with the sham group (p=0.012). During the blinded evaluation period, the mean seizure frequency in the treatment group was 22.4 (range, 0.0-226.8) and 29.8 (range, 0.3-44.46) in the sham group. The treatment group experienced a -37.9% change in seizure frequency (95% confidence interval [CI], -6.7% to -27.7%), while the sham 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). There were no significant differences between groups over the blinded evaluation period for secondary end points of responder rate (proportion of subjects who experienced at least a 50% reduction in mean disabling seizure frequency versus the pre-implant period), 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 preimplant 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 one year (p=0.001) and two years post-implant (p=0.016). For the study's primary safety end point, the significant adverse event rate over the first 28 days post-implant was 12%, which did not differ significantly from 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 did not differ significantly from the prespecified, literature-derived comparator of 36% for implantation and treatment with deep brain stimulation for Parkinson disease. The treatment and sham groups did not differ significantly in terms of mild or serious adverse events during the blinded evaluation period. Intracranial hemorrhage occurred in nine (4.7%) of 191 subjects; implant or incision site infection occurred in 10 (5.2%) of 191 subjects, and the devices were explanted from four of these subjects. The authors concluded responsive cortical stimulation may provide another treatment option for persons with medically intractable partial seizures. This study was funded by NeuroPace, Inc.

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 during the RNS System Pivotal Trial. Of the 191 subjects implanted, 182 subjects completed follow-up to one-year post-implant, and 175 subjects completed follow-up to two years post-implant. Six patients withdrew from the trial, four underwent device explantation due to infection, and six subjects died. Four deaths were attributed to possible or definite sudden, unexplained death in epilepsy (SUDEP); one of these subjects was randomized to the sham group and did not have stimulation enabled. One subject died of lymphoma and one of suicide. The subject who died of suicide had a preexisting history of depression but was clinically stable at the time of enrollment. During the open-label period, at two years of follow-up, median percent reduction in seizures was 53%, compared with the pre-implant baseline (p<0.001), and the responder rate (percentage of subjects with a 50% or more reduction in seizures) was 55%.

Loring et al. (2015) analyzed one of the trial's pre-specified safety end points (neuropsychologic function) during the Pivotal trial's open-label period. Neuropsychological testing focused on language and verbal memory, measured by the Boston Naming Test and the Rey Auditory Verbal Learning Test. A total of 175 patients had cognitive assessment scores at baseline and at one or two (or both) years and were included in this analysis. The authors used reliable change indices (RCIs) to identify patients with changes in test scores beyond that attributed to practice effects or measurement error in the test-retest setting, with 90% RCIs used for classification. Overall, no significant group-level declines in any neuropsychological outcomes were detected. On the Boston Naming Test, 23.5% of subjects demonstrated RCI improvements, while 6.7% had declines; on the Rey Auditory Verbal Learning Test, 6.9% of subjects demonstrated RCI improvements, and 1.4% demonstrated declines.

Meador et al. (2015) reported on quality of life and mood outcomes for individuals in the RNS pivotal trial. At the end of the blinded study period, both groups reported improvements in Quality of Life in Epilepsy Inventory-89 (QOLIE-89) scores, with no statistically significant differences between groups. In analysis of those with follow-up to two years post-enrollment, implanted patients had statistically significant improvements in QOLIE-89 scores from enrollment to one- and two-year follow-up. Mood, as assessed by the Beck Depression Inventory and the Profile of Mood States, did not worsen over time.

The Long-Term Treatment (LTT) Study was a seven-year, multicenter, prospective, open-label study to evaluate the RNS System's long-term efficacy and safety in individuals who participated in the device's feasibility or pivotal trials. Bergey et al. (2015) reported on follow-up for 191 subjects who participated in a two-year randomized, blinded, controlled study and 65 subjects who completed a two-year open label safety study (n=230) for a median 5.4 years. A total of 39 participants discontinued participation in the LTT Study, resulting in 191 active participants. For follow-up at years three and six, the median percent reductions in seizures were 60% and 66%, respectively. Responder rates were 58% and 59%

for year three and year six, respectively. Statistically significant quality of life improved at four years, with a trend toward improvement at five years. After five years, the sample sizes were not sufficient to reliably assess statistical significance. The most common adverse events were implant site infection (n=24 [9.4%]) and increase in complex focal seizures (n=20 [7.8%]). There were 11 deaths, seven of which were attributed to possible, probable, or definite SUDEP. The authors stated that the frequency of deaths, including deaths by SUDEP, was not greater than expected in patients with medically intractable partial onset seizures.

Nair et al. (2020) conducted a long-term, prospective, open-label study that included patients who participated in the two-year feasibility or pivotal studies of the RNS System between 2004 and 2018. Patients were followed up for an additional seven years. Overall, 230 patients enrolled in the study, and 162 completed all nine years of follow-up, providing a total of 1895 patient-implantation years. Among 68 patients who discontinued the study, 4 experienced emergent explants, five were lost to follow-up, nine were deceased, and 50 withdrew. The mean follow-up period was 7.5 years. At nine years, the median percent reduction in seizure frequency was 75% ($p<0.0001$), 73% of patients were considered responders, and 35% had at least 90% reduction in seizure frequency. Overall, 18.4% of patients experienced at least one year free of seizures. Overall scores for quality of life and epilepsy-targeted and cognitive domains of the Quality of Life in Epilepsy-89 inventory remained significantly improved at year 9 ($p<0.05$). The only device-related serious adverse events that were reported in at least 5% of patients were implantation site infection and elective explantation of the neurostimulator, leads, or both. Overall, serious device-related implantation site infection occurred in 12.1% of patients. No serious adverse events occurred related to stimulation.

Pediatrics

RNS is not FDA approved for patients younger than 18 years of age and published literature on children is limited. RNS has been used on an off-label basis in pediatric patients.

In 2023, the Pediatric Epilepsy Research Consortium (PERC) published findings from a multicenter, prospective, case series including data from 22 collaborating US pediatric epilepsy centers. Of 1,426 patients included in the comprehensive PERC surgery database at the time of analysis, 56 unique patients from 12 centers received RNS for focal drug resistant epilepsy not considered candidates for resective surgery. The mean age at RNS implantation was 14.9 years (range, 5.6 to 19.5 years; S.D., 3.7) with mean duration of epilepsy at the time of implantation of 8.1 years (range, 0.8 to 16.9 years; S.D., 3.9). Surgical complications occurred in three individual patients (5.3%) including one patient with a malpositioned lead and transient weakness and two patients who had transient weakness in relation to resection or subdural grid placement, not related to RNS placement. With a mean duration of follow-up of one year, 65% of the patients with RNS enabled experienced a >50% seizure reduction. The authors acknowledged that there are important limitations in generalizing the findings from this study and that randomized controlled studies of RNS in children are necessary to understand the efficacy and safety in this vulnerable population.

NeuroPace is sponsoring the RESPONSE Study, which is a prospective, open-label, single-arm study to evaluate the efficacy and safety of the RNS System in individuals aged 12 through 17-year-olds (NCT04839601). The expected completion date is in December 2027.

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*
- *Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).*

CPT Codes

Code	Description
61850	Twist drill or burr hole(s) for implantation of neurostimulator electrodes, cortical

Code	Description
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
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 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
95970	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 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
95983	Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact groups[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 neurostimulator pulse generator/transmitter programming, first 15 minutes face-to-face time with physician or other qualified health care professional
95984	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)

HCPCS Codes

Code	Description
C1767	Generator, neurostimulator (implantable), nonrechargeable
L8686	Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension
L8688	Implantable neurostimulator pulse generator, dual array, non- rechargeable, includes extension

ICD10 Codes

Code	Description
G40.011 - G40.019	Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset, intractable (code range)
G40.111 - G40.119	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, intractable (code range)
G40.211 - G40.219	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, intractable (code range)
Investigational Codes:	
All other ICD10 diagnosis codes are considered investigational.	

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*Key Article

KEY WORDS

NeuroPace, RNS, Epilepsy, Seizures

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

Based on our review, responsive neurostimulation is not addressed in National or Regional Medicare coverage determinations or policies.