Molina Clinical Policy
Responsive Neurostimulation (RNS) for Epilepsy: Policy No. 430

Last Approval: 04/10/2024
Next Review Due By: April 2025

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

Epilepsy is one of the most common neurological conditions worldwide characterized by recurrent seizures. Seizures are defined as paroxysmal disorders of the central nervous system characterized by abnormal cerebral neuronal discharge, with or without loss of consciousness. Most seizures can be categorized as either focal or generalized according to whether the onset of electrical activity involves both sides or a focal region of the brain. Epilepsy has a myriad of causes, such as brain tumors, metabolic disorders, hypoxic brain injuries, strokes, infections, and certain genetic syndromes; however, most cases are idiopathic in origin. Anti-epileptic medications are the first line of defense in treating the seizure disorder, however, many cases remain uncontrolled even in the setting of a rigorous drug regimen. Since epilepsy carries an increased risk for premature death, controlling the condition is paramount to patient's overall health and wellbeing.

Refractory epilepsy, also referred to as intractable or drug-resistant epilepsy, is used to characterize patients with epilepsy whose seizures do not effectively respond to anti-epileptic medications. Refractory epilepsy may affect up to 20 to 40% of epileptic patients, or about 400,000 persons in the United States, the majority of which present with partial/focal-onset seizures, especially those associated with temporal lobe epilepsy (Gummadavelli et al. 2022; Sirven 2022). Recent International League Against Epilepsy expert consensus recommendations support early referral for epilepsy resective surgery for patients with refractory epilepsy as soon as drug resistance is established, regardless of epilepsy duration, seizure type, epilepsy type, localization, or comorbidities (Jehi et al. 2022). When surgery is contraindicated or ineffective, however, neuromodulation has emerged as a treatment option.

Responsive Neurostimulation (RNS) is an epileptic treatment which involves the surgical implantation of a neurostimulator device. The closed – loop device can detect specific patterns of epileptogenic activity and delivering focal stimulation to abort seizure activity. The device consists of a cranially implanted, programmable cortical neurostimulator that senses and records brain activity through electrode-containing leads that are placed at the seizure focus. The system is intended to reduce the frequency of seizures in individuals with medically refractory epilepsy that persists in severity and/or frequency despite a reasonable trial of two or more antiepileptic medications.

Regulatory Status

RNS is a procedure and thus not regulated by the FDA. Any medical devices, drugs, and/or tests used as part of this procedure, on the other hand, may be subject to FDA regulation.

Neuropace Inc's (Mountain View, CA) NeuroPace RNS System is the only FDA approved RNS system for patients with refractory partial epilepsy. It received Premarket Approval in November 2013 under the product code PFN (Implanted brain stimulator for epilepsy) and PMA number P100026. It is indicated "as an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures who have undergone diagnostic testing that localized no more than 2 epileptogenic foci, are refractory to two or more antiepileptic medications, and currently have frequent and disabling seizures (motor partial seizures, complex partial seizures and/or secondarily generalized seizures). The RNS® System has demonstrated safety and effectiveness in patients who average 3 or more disabling seizures per month over the three most recent months (with no month with fewer than two seizures) and has not been evaluated in patients with less frequent seizures."

Per the "malfunction" and "injury" reports in the FDA Manufacturer and User Facility Device there had been 11 deaths in the RNS trials as of October 24, 2012, including the RNS System Pivotal Study and the long-term treatment study. Two of the deaths were suicides (1 in each of the pivotal and long-term therapy studies), one was caused by lymphoma, one was caused by status epilepticus complications, and seven were caused by prospective, probable, or definite sudden unexplained death in epilepsy. The projected rate of unexpected unexplained mortality in epilepsy is 5.9 per 1000 implant years with 1,195 patient implant years, which is equal to the expected rate for patients with refractory epilepsy.

RELATED POLICIES

MCP-335: Deep Brain Stimulation (DBS) for Epilepsy
MCP-006: Vagal Nerve Stimulation (VNS) for Epilepsy

COVERAGE POLICY

The insertion of Responsive Neurostimulation (e.g., NeuroPace RNS System) **may be considered medically necessary** when **ALL** the following clinical criteria with documentation are met:

1. Member is 18 years or older
2. Diagnosis of focal epilepsy
3. Comprehensive diagnostic testing identified 1 or 2 localized epileptogenic foci
4. Average of three or more disabling seizures (e.g., motor focal seizures, complex focal seizures, or secondary generalized seizures) per month over the past 3 months
5. Refractory to two or more antiepileptic medications at therapeutic doses
6. Member is **ineligible** for any of the following:
    a. Focal resection epilepsy surgery (e.g., have an epileptic focus near the eloquent cerebral cortex; have bilateral temporal epilepsy)
    b. Vagus nerve stimulation.
7. Member is free All the following contraindications to responsive neurostimulation
    a. Younger than 18 years of age.
    b. High risk factors for surgical complications such as active systemic infection, coagulation disorders (such as the use of anti-thrombotic therapies) or platelet count below 50,000.
    c. Medical devices implanted that deliver electrical energy to the brain.
    d. Unable, or do not have the necessary assistance, to properly operate the NeuroPace® Remote Monitor or magnet.
8. Surgery is performed at a *Level 4 epilepsy center, in accordance with NAEC guidelines

The revision or replacement of Responsive Neurostimulation (e.g., NeuroPace RNS System) (generator, leads, and/or battery) **may be considered medically necessary** when **ALL** the following clinical criteria with documentation are met:

1. Member meets all criteria (1 - 8) as stated above
2. Member's current device is no longer under warranty and cannot be repaired.

LIMITATIONS AND EXCLUSIONS

The following are considered **exclusions** for RNS placement (safety and effectiveness of the RNS® System has not been established):

1. Generalized epilepsy.

2. Simple partial sensory seizures only.
3. Less than three seizures a month on average.
4. 3 or more epileptic foci.
5. Failure of less than 2 antiepileptic drugs.
6. Seizure focus that cannot be adequately localized.
7. Pregnant women or nursing mothers.
8. Pediatrics (under the age of 18).

The following are considered **experimental, investigational, and unproven** based on insufficient evidence:

1. Any indications other than those listed above.

ADMINISTRATION:

1. The RNS® System should only be used by neurologists or neurosurgeons with adequate experience in the management of intractable epilepsy and in the localization of epileptic foci, including the use of scalp and intracranial electrodes (Neuropace, 2020).
2. RNS is typically performed as an outpatient procedure for the treatment of refractory partial epilepsy and is only authorized as an inpatient procedure in exceptional circumstances, such as the presence of a co-morbid condition that necessitates monitoring in a more controlled environment, such as the inpatient setting.

SUMMARY OF MEDICAL EVIDENCE

Skrehot et al. (2023) conducted a systemic review and meta-analysis of comparing different neuro stimulation techniques in focal epilepsy. There are no head-to-head comparison RCTs between the three techniques of vagal nerve stimulation (VNS), deep brain stimulation (DBS), and responsive neurostimulation (RNS), therefore the authors pooled data to compare seizure reduction efficacy for focal epilepsy. Of the data found, sufficient data was available at years one (n = 642), two (n = 480), and three (n = 385) for comparing the three modalities with each other. Seizure reduction for the devices at years one, two, and three respectively were: RNS: 66.3%, 56.0%, 68.4%; DBS- 58.4%, 57.5%, 63.8%; VNS 32.9%, 44.4%, 53.5%. Seizure reduction at year one was greater for RNS ($p < 0.01$), and DBS ($p < 0.01$) compared to VNS, though the differences diminished with longer follow up time.

Kusyk et al. (2022) conducted a systematic review and meta – analysis of responsive neurostimulation in epilepsy. Seventeen studies were included, totaling 541 patients. Mean seizure reduction rate was 68% (95% confidence interval 61%-76%), and the mean responder rate was 68% (95% confidence interval 60%-75%). Complications occurred in 102 of 541 patients, for a complication rate of 18.9%. The authors did note that a strong publication bias toward greater seizure reduction rate and increased responder rate was demonstrated among included literature; therefore, while current RNS treatment data is optimistic it should be interpreted cautiously.

Touma et al. (2022) conducted a systematic review and meta-analysis evaluating the mean percentage of seizure frequency decrease as compared to baseline, as well as proportion of treatment responders and those with seizure freedom. Thirty studies were included, 6 of which were RCTs. At long-term follow-up (mean 1.3 years), five observational studies for VNS reported a pooled mean percentage decrease in seizure frequency of 34.7% (95% confidence interval [CI]: -5.1, 74.5). In the open-label extension studies for RNS, the median seizure reduction was 53%, 66%, and 75% at 2, 5, and 9 years of follow-up, respectively. For DBS, the median reduction was 56%, 65%, and 75% at 2, 5, and 7 years, respectively. The proportion of individuals with seizure freedom at last follow-up increased significantly over time for DBS and RNS, whereas a positive trend was observed for VNS. Quality of life was improved in all modalities. The most common complications included hoarseness, and cough and throat pain for VNS and implant site pain, headache, and dysesthesia for DBS and RNS. The authors concluded that neurostimulation is an effective treatment for refractory epilepsy with few major complications. Seizure-reduction rates among the three therapies were similar during the initial blinded phase with promising long term follow-up studies are for RNS and DBS, however encouraging long term follow up is lacking for VNS.

The RNS Pivotal Trial

Morrell (2011) reported on the pivotal study which assessed the safety and efficacy of RNS System for patients with drug-resistant and focal onset epilepsy. The two-year multicenter, double-blind, RCT of 191 adults (n = 191) with refractory focal seizures with or without secondary generalization (RNS System in Epilepsy Study Group). Participants were adults (18-70 years of age), had focal onset seizures that were left uncontrolled in ≥2 trials of antiepileptic drugs,

suffered 3≥ disabling seizures per month on average, and had up to two epileptogenic regions. Of those enrolled, 32% had prior epilepsy surgery and 34% previously had VNS, which was turned off or explanted before enrollment. All participants had the RNS implantation procedure but were randomly assigned to activated and nonactivated groups and followed for the 12-week blinded treatment phase, then an 84-week open-label period where all subjects received active therapy. After a 4-week period during which no patients' systems were activated to control for any temporary insertion effect, those in the activated group had RNS activated for 12 weeks. After the initial 12 weeks all patients' systems were activated, and patients were followed on an open-label basis. 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 vs. 27% in the sham group. However, seizure-free days 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 vs. 16% fewer days in the sham group (p=0.048). The difference between the two groups had widened at 5 months after implantation with disappearance of the lesioning effect. The reduction rate in seizure frequency was significantly better in patients receiving stimulation by the RNS System than in the sham group (41.5% vs 9.4%, p = 0.008). The serious adverse event rate for medical and surgical events for the first 84 weeks was 18.3%. The authors concluded that this pivotal RCT presents Class I evidence that responsive cortical stimulation is effective in reducing the frequency of disabling partial onset seizures that were refractory to antiepileptic drugs and, in many cases, vagus nerve stimulation or epilepsy surgery.

Heck et al. (2014) published the final 2-year results of the pivotal trial. The active group had a -37.9% change in seizures and the sham group had a -17.3% change (p=0.012) at the end of the blinded period. In the open-label period, the median percent reduction in seizures was 44% at 1 year and 53% at 2 years, indicating a progressive and significant improvement over time. The authors found no differences in the rate of serious adverse events between groups, which was consistent with the known risks of an implanted medical device, seizures, and other epilepsy treatments. No adverse events on neuropsychological function or mood were observed.

The Long-Term Treatment (LTT) Study is an ongoing 7-year multicenter prospective open-label study to evaluate the long-term efficacy and safety of the RNS System in participants who had completed the feasibility or pivotal studies (Nair et al. 2020). It is reported based on 9 years of patient follow-up and is the largest multicenter prospective trial in the field of neuromodulation to date. During the open-label period of the pivotal trial and the ensuing long-term treatment trial, all the patients received responsive stimulation and experienced progressive decrease in their seizure rates (Bergey et al. 2015; Heck et al. 2014; Nair et al. 2020). Adverse event and daily seizure diary data were collected every 6 months at a minimum. Antiepileptic medications were adjusted as medically necessary. Efficacy was assessed as median percent change in seizures and as responder rate (the percentage of participants with a 50% or greater reduction in seizures) for each 3-month period compared to the preimplant baseline. According to the results of the LTT study, efficacy is maintained over time supported by the results at 9 years in which 230 individuals treated with the RNS System showed a 75% reduction in debilitating seizures, improvements in quality of life (including cognition), and no chronic stimulation-related side effects (Nair et al. 2020). The reduction rate in seizure frequency was 44% at 1 year, 53% at 2 years, 60-66% at 3-6 years, and 75% at 9 years (Bergey et al. 2015; Heck et al. 2014; Nair et al. 2020).

National and Specialty Organizations

Currently there are no guidelines or position statements specifically addressing the use of NeuroPace or RNS for drug-resistant epilepsy.

CODING & BILLING INFORMATION

CPT (Current Procedural Terminology) Codes

Code	Description
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	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus,

	periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; each additional array (List separately in addition to primary procedure)
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	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; 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
95983	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 neurostimulator pulse generator/transmitter programming, first 15 minutes face-to-face time with physician or other qualified health care professional
95984	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 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)

HCPCS (Healthcare Common Procedure Coding System) Codes

Code	Description
C1767	Generator, neurostimulator (implantable), non-rechargeable
C1778	Lead, neurostimulator (implantable)
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

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

04/10/2024 Policy reviewed. No changes to coverage criteria.
04/13/2023 New policy. IRO Peer Review on March 10, 2023, by a practicing, board-certified physician with a specialty in Neurological Surgery.

REFERENCES

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