Molina Clinical Policy
Responsive Neurostimulation for the Treatment of Refractory Partial Epilepsy (NeuroPace®): Policy No. 430

Last Approval: 4/13/2023
Next Review Due By: April 2024

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

Drug-resistant epilepsy (DRE), also called intractable, medically refractory, or pharmacoresistant epilepsy, is used to describe patients with epilepsy whose seizures do not respond well to antiseizure medications, also called antiepileptic drugs (Sirven, 2022). Medically refractory epilepsy may affect up to 20% to 40% of epileptic patients, or about 400,000 persons in the United States (NINDS, 2018; Sirven, 2022). The International League Against Epilepsy (ILAE) refers to drug-resistant epilepsy as the failure of adequate trials of two tolerated, appropriately chosen, and used antiseizure medications schedules, whether as monotherapy or in combination, to achieve sustained seizure freedom (Kwan, 2010). Epilepsies presenting with partial or focal-onset seizures, especially those associated with temporal lobe epilepsy, are overrepresented among DRE (Asadi-Pooya et al., 2017; Gummadavelli et al., 2022). Resective epilepsy surgery is the preferred treatment for DRE patients. Recent ILAE expert consensus recommendations support early referral for epilepsy surgery for patients with DRE (if adherent to management) up to 70 years of age, as soon as drug resistance is established and regardless of epilepsy duration, seizure type, epilepsy type, localization, or comorbidities (Jehi et al., 2022). However, when resective surgery is contraindicated or ineffective, neurostimulation has emerged as a treatment option (AANS, 2023). There are three neuromodulation approaches: vagus nerve stimulation, responsive neurostimulation, and deep brain stimulation. Head-to-head comparison trials have not been conducted in comparable patient populations with focal epilepsy.

Responsive Neurostimulation (RNS) is based on a closed-loop device capable of detecting specific patterns of epileptogenic activity and delivering focal stimulation to abort seizure activity. The RNS System continuously monitors neural electroencephalography (EEG) activity at the possible seizure onset zone where electrodes are placed and responds with electrical stimulation when a pre-defined epileptic activity is detected. One device, the NeuroPace RNS System (NeuroPace®) is currently approved by the Food and Drug Administration (FDA) and is commercially available. NeuroPace® 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. According to the manufacturer, the device provides “responsive cortical stimulation,” which senses and records seizure activity and responds according to a pre-set program. 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. The NeuroPace RNS® System was approved through the premarket approval process (FDA product code: PFN) in November 14, 2013 for the following indications (Premarket Approval Number P100026):

> “The RNS® System is an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures who have undergone diagnostic testing that localized no more than 2 epileptogenic foci, are refractory to two or more antiepileptic medications, and currently have frequent and disabling seizures (motor partial seizures, complex partial seizures and/ or secondarily generalized seizures). The RNS® System has demonstrated safety and effectiveness in patients who average 3 or more disabling seizures per month over the three most recent months (with no month with fewer than two seizures) and has not been evaluated in patients with less frequent seizures.”

This policy addresses RNS for the treatment of refractory partial epilepsy (e.g., the NeuroPace® RNS® System). Neurostimulation.

RELATED POLICIES

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

COVERAGE POLICY

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

A. Insertion of RNS

1. Diagnosis of focal epilepsy; **AND**
2. Comprehensive diagnostic testing identified 1 or 2 localized epileptogenic foci; **AND**
3. Average of **THREE** or more disabling seizures (e.g., motor focal seizures, complex focal seizures, or secondary generalized seizures) per month over the 3 recent months; **AND**
4. Refractory to **TWO** or more antiepileptic medications at therapeutic doses; **AND**
5. 18 years or older; **AND**
6. Member is **not** a candidate 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); **OR**
   b. Vagus nerve stimulation.
7. No contraindications for responsive neurostimulation device placement
8. Surgery is performed at a *Level 4 epilepsy center, in accordance with NAEC guidelines.
   *Epilepsy Center Locations and Designation (NAEC, 2023)

B. Revision or Replacement of RNS

A replacement or revision of a RNS device (generator, leads, and/or battery) may be deemed medically necessary for a patient who meets **ALL** the criteria (in #A above) and whose current device is no longer under warranty and cannot be repaired.

LIMITATIONS AND EXCLUSIONS

The following are considered **contraindications/exclusions** for RNS placement:

1. Younger than 18 years of age.
2. 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.
3. Medical devices implanted that deliver electrical energy to the brain.
4. Unable, or do not have the necessary assistance, to properly operate the NeuroPace® Remote Monitor or magnet.

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

The RNS System appears to reduce seizure frequency in adults with intractable epilepsy, according to evidence from a single randomized controlled trial (RCT) and long-term follow-up of the pivotal RCT. Serious adverse events (AEs) have been reported.

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 AE 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.

There is no adequate evidence for RNS use in pediatric age. The published data shows no difference in the frequency of AEs between the group of patients treated with the RNS System and the group of patients with sham treatment during the blinded treatment period in the pivotal trial (Morrell, 2011).

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, 2015; Heck, 2014; Nair et al., 2020). AE 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, 2015; Heck, 2014; Nair et al., 2020).

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 AEs between groups, which was consistent with the known risks of an implanted medical device, seizures, and other epilepsy treatments. No AEs on neuropsychological function or mood were observed.

Bergey et al., 2015 reported that two years after implantation, the median reduction in seizures among 256 adult patients was 53%. The median percent seizure reduction in the RCT was 44% at 1 year and 53% at 2 years, and ranged from 48% to 66% in postimplant years 3 through 6. Quality of life improvements were maintained. Over the course of 5.4 years, the most common serious device-related AEs were implant site infection (9.0%) involving soft tissue and neurostimulator explantation (4.7%).

The FDA summarized deaths and adverse events in its summary of safety and effectiveness data for the RNS. According to the safety and effectiveness data, 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.

Refer to the FDA Manufacturer and User Facility Device database (product code: PFN) for reports of “Malfunction” and “Injury”.

An Evolving Evidence Review on the NeuroPace RNS System (NeuroPace Inc.) for Treatment of Drug-Resistant Epilepsy published in September 2021 concluded that current evidence reduces seizure frequency in adults with intractable epilepsy. However, there have been reports of serious AEs (Hayes, 2021).

Gooneratne et al. (2016) conducted a systematic review comparing neurostimulation technologies in refractory focal epilepsy. A literature search was conducted for studies with long-term efficacy data (for at least 5 years) and at least 30 patients evaluating vagus nerve stimulation, cortical responsive stimulation, or deep brain stimulation in refractory focal or focal epilepsy through November 2015. No direct comparisons were found between the technologies. The only responsive neurostimulation study included was the previously described RNS System Pivotal Study. Indirect comparisons of the technologies were limited by differences in RCT inclusion criteria, definitions of response, and methods of data collection between studies. All three neurostimulation technologies were found to be long-term effective, with progressively better seizure control over time, according to the reviewers.

National and Specialty Organizations

There were no guidelines or position statements specifically addressing the use of NeuroPace or RNS for drug-resistant epilepsy.

SUPPLEMENTAL INFORMATION

Partial Seizures, Partial Onset Seizures, or Focal Onset Seizures originate from a discrete area of the brain, where they may stay confined or spread to other areas. Partial seizures may be simple or complex. Simple partial seizures, unlike complex partial seizures, are not associated with changes in consciousness. When partial seizures spread to

both sides of the brain, secondary generalization occurs, resulting in tonic-clonic seizures and loss of consciousness. Partial seizures, especially when they originate on the medial surface of the frontal lobe, can quickly spread across the midline through the corpus callosum and become generalized. Partial seizures are characterized by motor, sensory, autonomic, or psychic symptoms during which consciousness is preserved and can cause a range of different symptoms, depending on the seizure type and the brain area involved. Clinical signs and symptoms of focal seizures relate to the affected area of the brain (the ictal focus). Thirty percent to 40% of patients with partial-onset seizures have intractable epilepsy, defined by the ILAE as a failure to control seizures after two seizure medications that have been appropriately chosen and used (Heck, 2014)

CODING & BILLING INFORMATION

CPT	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)
61867	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), with use of intraoperative microelectrode recording; first array
61868	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, Globus pallidum, subthalami nucleus, periventricular, periaqueductal gray), with 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

HCPCS Codes

HCPCS	Description
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

4/13/2023	New policy. IRO Peer Review on March 10, 2023 by a practicing, board-certified physician with a specialty in Neurological Surgery.

REFERENCES

Government Agencies

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   - *No National Coverage Determinations (NCDs) were identified on the CMS website addressing coverage for the NeuroPace RNS System for drug-resistant epilepsy.*
2. United States Food and Drug Administration (FDA). Premarket approval (PMA) for neuropace RNS system. Updated 02/27/2023. Accessed March 2023. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P100026.

Peer Reviewed Publications

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National and Specialty Organizations

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2. Epilepsy Foundation. FDA approves responsive neurostimulation therapy by NeuroPace. Published November 13, 2014. https://www.epilepsy.com/stories/fda-approves-responsive-neurostimulation-therapy-neuropace.
3. Epilepsy Foundation. Responsive neurostimulation (RNS). 2023. https://www.epilepsy.com/treatment/devices/responsive-neurostimulation.
4. National Association of Epilepsy Centers (NAEC). All epilepsy center locations. Accessed January 2023. https://www.naec-epilepsy.org/about-epilepsy-centers/find-an-epilepsy-center/all-epilepsy-center-locations/.

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1. Neuropace. RNS System Clinical Summary. Updated June 2020. Available from Neuropace. Updated June 2020. Accessed March 2023.

Other Authoritative Publications

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