MEDICAL POLICY

POLICY TITLE	RESPONSIVE NEUROSTIMULATION FOR THE TREATMENT OF REFRACTORY FOCAL EPILEPSY
POLICY NUMBER	MP 1.156

CLINICAL BENEFIT	☒ MINIMIZE SAFETY RISK OR CONCERN. ☐ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**2/1/2025**

I. POLICY

Responsive neurostimulation may be considered **medically necessary** for individuals with focal epilepsy who meet **all** of the following criteria:

- Are 18 years or older; **and**
- Have a diagnosis of focal seizures with 1 or 2 well-localized seizure foci identified; **and**
- Have an average of 3 or more disabling seizures (e.g., motor focal seizures, complex focal seizures, or secondary generalized seizures) per month over the prior 3 months; **and**
- Are refractory to medical therapy (have failed ≥2 appropriate antiepileptic medications at therapeutic doses); **and**
- Are not candidates for focal resective epilepsy surgery (e.g., have an epileptic focus near the eloquent cerebral cortex; have bilateral temporal epilepsy); **and**
- Do not have contraindications for responsive neurostimulation device placement (see Policy Guidelines section).

Responsive neurostimulation is considered **investigational** for all other indications. All other indications of responsive neurostimulation other than those described in the policy section are considered investigational, as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

POLICY GUIDELINES

Contraindications for responsive neurostimulation device placement include 3 or more specific seizure foci, presence of primary generalized epilepsy, or presence of a rapidly progressive neurologic disorder.

II. PRODUCT VARIATIONS

TOP

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO:

Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:

https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies .

III. DESCRIPTION/BACKGROUND

TOP

Approximately one-third of individuals with epilepsy do not respond to typical first-line therapy with antiepileptic medications. Seizures that occur in these individuals are referred to as refractory or drug-resistant. In individuals with refractory epilepsy, combination antiepileptic therapy often results in increased risk of adverse events. Other nonpharmacologic treatment options are available, including surgical approaches, ketogenic diet, and responsive neurostimulation. One responsive neurostimulation device, the NeuroPace RNS System, has U.S. Food and Drug Administration (FDA) approval for the treatment of refractory focal (formerly partial) epilepsy.

Medical Therapy for Focal Seizures

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. Standard therapy for seizures, including focal seizures, includes treatment with 1 or more of various antiepileptic drugs, which include newer antiepileptic drugs, such as oxcarbazepine, lamotrigine, topiramate, gabapentin, pregabalin, levetiracetam, tiagabine, and zonisamide. Currently, response to antiepileptic drugs is less than ideal: 1 systematic review comparing newer antiepileptic drugs for refractory focal epilepsy reported an overall average responder rate in treatment groups of 34.8%. As a result, a substantial number of individuals 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, a randomized controlled trial has 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 5-

year freedom from seizure rates of 52%, with 28% of seizure-free individuals able to discontinue antiepileptic drugs. Selection of appropriate individuals for epilepsy surgery is important, because those with nonlesional extratemporal lobe epilepsy have worse outcomes after surgery than those with nonlesional temporal lobe epilepsy. Some individuals 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 neurologic 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 has been widely used for refractory epilepsy, following U.S. Food and Drug Administration (FDA) approval of a vagus nerve stimulation device in 1997 and 2 randomized controlled trials evaluating vagus nerve stimulation in epilepsy. Although the mechanism of action for vagus nerve stimulation is not fully understood, vagus nerve stimulation is thought to 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 of deep brain nuclei (deep brain stimulation) involves the use of chronic, continuous stimulation of a target. It has been most widely used in the treatment of Parkinson disease and other movement disorders and has been investigated for treating epilepsy. Deep brain stimulation of the anterior thalamic nuclei was studied in a randomized control trial, the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy trial, but deep brain stimulation 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

Responsive neurostimulation shares some features with deep brain stimulation but is differentiated by its use of direct cortical stimulation and by its use in both monitoring and stimulation. The responsive neurostimulation system provides stimulation in response to detection of specific epileptiform patterns, while deep brain stimulation provides continuous or intermittent stimulation at preprogrammed settings.

Development of the responsive neurostimulation system arose from 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. Individuals 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.[8,

In tandem with the recognition that cortical stimulation can stop epileptiform discharges was development of fast pre-ictal seizure prediction algorithms. These algorithms interpret electrocorticographic data from detection leads situated over the cortex. The responsive neurostimulation process thus includes electrocorticographic monitoring via cortical electrodes, analysis of data through a proprietary seizure detection algorithm, and delivery of electrical stimulation via both cortical and deep implanted electrodes in an attempt to halt a detected epileptiform discharge.

One device, the NeuroPace RNS® System, is currently approved by FDA and is commercially available.

Responsive Neurostimulation for Seizure Monitoring

Although the intent of the electrocorticography component of the responsive neurostimulation system is to provide input as a trigger for neurostimulation, it also provides continuous seizure mapping data (chronic unlimited cortical electrocorticography) that may be used by practitioners to evaluate individuals' seizures. In particular, the seizure mapping data have been used for surgical planning of individuals who do not experience adequate seizure reduction with responsive neurostimulation placement. Several studies have described the use of responsive neurostimulation in evaluating seizure foci for epilepsy surgery[9,] or for identifying whether seizure foci are unilateral.

This review does not further address use of responsive neurostimulation exclusively for seizure monitoring.

Regulatory Status

In November 2013, the NeuroPace RNS System (NeuroPace) was approved by the FDA through the premarket approval process for the following indication.

“The RNS System is an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures who have undergone diagnostic testing that localized no more than 2 epileptogenic foci, are refractory to two or more antiepileptic medications, and currently have frequent and disabling seizures (motor partial seizures, complex partial seizures and/ or 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.”

FDA product code: PFN.

IV. RATIONALE

TOP

SUMMARY OF EVIDENCE

This evidence review was created in November 2014 with searches of the PubMed database. The most recent literature update was performed through February 22, 2024.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to individuals and to managing the course of that condition. Validated outcome measures are necessary 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.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

V. DEFINITIONS

TOP

NA

VI. BENEFIT VARIATIONS

TOP

The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member’s health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits, and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and

providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

TOP

This is a new treatment. This policy may be subject to change due to additional data, information and feedback received. Please check for updates.

Capital Blue Cross' medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

TOP

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

Procedure Codes							
L8680	L8686	L8688	61850	61860	61863	61864	61880
61885	61886	61888	61889	61891	61892	95970	95971

ICD-10-CM Diagnosis Code	Description
G40.001	Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset, not intractable, with status epilepticus
G40.009	Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset, not intractable, without status epilepticus
G40.011	Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset, intractable, with status epilepticus

ICD-10-CM Diagnosis Code	Description
G40.019	Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset, intractable, without status epilepticus
G40.101	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, not intractable, with status epilepticus
G40.109	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, not intractable, without status epilepticus
G40.111	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, intractable, with status epilepticus
G40.119	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, intractable, without status epilepticus
G40.201	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, not intractable, with status epilepticus
G40.209	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, not intractable, without status epilepticus
G40.211	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, intractable, with status epilepticus
G40.219	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, intractable, without status epilepticus
G40.841	KCNQ2-related epilepsy, not intractable, with status epilepticus
G40.842	KCNQ2-related epilepsy, not intractable, without status epilepticus
G40.843	KCNQ2-related epilepsy, intractable, with status epilepticus
G40.844	KCNQ2-related epilepsy, intractable, without status epilepticus
G40.C01	Lafora progressive myoclonus epilepsy, not intractable, with status epilepticus
G40.C09	Lafora progressive myoclonus epilepsy, not intractable, without status epilepticus
G40.C11	Lafora progressive myoclonus epilepsy, intractable, with status epilepticus
G40.C19	Lafora progressive myoclonus epilepsy, intractable, without status epilepticus

IX. REFERENCES

TOP

1. *Costa J, Fareleira F, Ascenção R, et al. Clinical comparability of the new antiepileptic drugs in refractory partial epilepsy: a systematic review and meta-analysis. Epilepsia. Jul 2011; 52(7): 1280-91. PMID 21729036*
2. *Wiebe S, Blume WT, Girvin JP, et al. A randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med. Aug 02 2001; 345(5): 311-8. PMID 11484687*

3. *de Tisi J, Bell GS, Peacock JL, et al. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. Lancet. Oct 15 2011; 378(9800): 1388-95. PMID 22000136*
4. *Noe K, Sulc V, Wong-Kisiel L, et al. Long-term outcomes after nonlesional extratemporal lobe epilepsy surgery. JAMA Neurol. Aug 2013; 70(8): 1003-8. PMID 23732844*
5. *Fridley J, Thomas JG, Navarro JC, et al. Brain stimulation for the treatment of epilepsy. Neurosurg Focus. Mar 2012; 32(3): E13. PMID 22380854*
6. *Fisher RS. Therapeutic devices for epilepsy. Ann Neurol. Feb 2012; 71(2): 157-68. PMID 22367987*
7. *Kossoff EH, Ritzl EK, Politsky JM, et al. Effect of an external responsive neurostimulator on seizures and electrographic discharges during subdural electrode monitoring. Epilepsia. Dec 2004; 45(12): 1560-7. PMID 15571514*
8. *Anderson WS, Kossoff EH, Bergey GK, et al. Implantation of a responsive neurostimulator device in patients with refractory epilepsy. Neurosurg Focus. Sep 2008; 25(3): E12. PMID 18759613*
9. *DiLorenzo DJ, Mangubat EZ, Rossi MA, et al. Chronic unlimited recording electrocorticography-guided resective epilepsy surgery: technology-enabled enhanced fidelity in seizure focus localization with improved surgical efficacy. J Neurosurg. Jun 2014; 120(6): 1402-14. PMID 24655096*
10. *King-Stephens D, Mirro E, Weber PB, et al. Lateralization of mesial temporal lobe epilepsy with chronic ambulatory electrocorticography. Epilepsia. Jun 2015; 56(6): 959-67. PMID 25988840*
11. *Spencer D, Gwinn R, Salinsky M, et al. Laterality and temporal distribution of seizures in patients with bitemporal independent seizures during a trial of responsive neurostimulation. Epilepsy Res. Feb 2011; 93(2-3): 221-5. PMID 21256715*
12. *Food and Drug Administration. Summary of Safety and Effectiveness Data: RNS System 2013*
13. *Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia. Apr 2017; 58(4): 522-530. PMID 28276060*
14. *Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. Jun 2010; 51(6): 1069-77. PMID 19889013*
15. *Xue-Ping W, Hai-Jiao W, Li-Na Z, et al. Risk factors for drug-resistant epilepsy: A systematic review and meta-analysis. Medicine (Baltimore). Jul 2019; 98(30): e16402. PMID 31348240*
16. *Neuropace, Inc. RNS(R) System Physician Manual for the RNS(R) Neurostimulator Model RNS-320. Revised February 2020.*
17. *Morrell MJ, King-Stephens D, Massey AD, et al. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology. Sep 27 2011; 77(13): 1295-304. PMID 21917777*
18. *Heck CN, King-Stephens D, Massey AD, et al. Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: final*

results of the RNS System Pivotal trial. Epilepsia. Mar 2014; 55(3): 432-41. PMID 24621228

19. *Loring DW, Kapur R, Meador KJ, et al. Differential neuropsychological outcomes following targeted responsive neurostimulation for partial-onset epilepsy. Epilepsia. Nov 2015; 56(11): 1836-44. PMID 26385758*
20. *Meador KJ, Kapur R, Loring DW, et al. Quality of life and mood in patients with medically intractable epilepsy treated with targeted responsive neurostimulation. Epilepsy Behav. Apr 2015; 45: 242-7. PMID 25819949*
21. *Nair DR, Laxer KD, Weber PB, et al. Nine-year prospective efficacy and safety of brain-responsive neurostimulation for focal epilepsy. Neurology. Sep 01 2020; 95(9): e1244-e1256. PMID 32690786*
22. *Skrehot HC, Englot DJ, Haneef Z. Neuro-stimulation in focal epilepsy: A systematic review and meta-analysis. Epilepsy Behav. May 2023; 142: 109182. PMID 36972642*
23. *Blue Cross Blue Shield Association Medical Policy Reference Manual. 7.01.143, Responsive Neurostimulation for the Treatment of Refractory Focal Epilepsy, May, 2024.*

X. POLICY HISTORY

TOP

MP 1.156	**04/10/2020 Major Review**. New policy adopted from BCBSA to provide coverage criteria for neurostimulation in patients with epilepsy refractory to other treatment.
	05/21/2021 Consensus Review. BCBSA full adoption. No change to policy statement. Coding and References reviewed.
	06/17/2021 Consensus Review. No changes to policy statement. FEP and references updated. Coding reviewed.
	08/23/2023 Administrative Update. New ICD 10 codes added to the policy.
	12/12/2023 Administrative Update. Added codes 61889, 61891, and 61892 as MN, effective 1/1/2024.
	01/10/2024 Consensus Review. Updated rationale, references. Coding reviewed, no changes.
	09/12/2024 Administrative Update. Added 4 new ICD-10 codes, effective 10/1/24.
	10/04/2024 Consensus Review. No changes to policy statement. Updated background, rational, references. Coding reviewed, no changes.

Top