Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
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Plan: Keystone First	**Submission Date**: 7/1/224
Policy Number: ccp.1515	**Effective Date:** 7/2022 **Revision Date:** June 1, 2024
Policy Name: Vagus nerve stimulation for post-stroke upper limb rehabilitation	

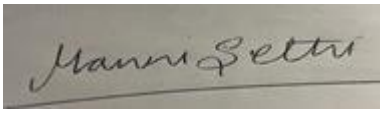
Type of Submission – Check all that apply:

New Policy
X Revised Policy*
Annual Review – No Revisions
Statewide PDL

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any clarifying information for the policy below:

See tracked changes below.

Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	**Signature of Authorized Individual:** 

Vagus nerve stimulation for post-stroke upper limb rehabilitation

Clinical Policy ID: CCP.1515

Recent review date: 6/2024

Next review date: 10/2025

Policy contains: Rehabilitation; stroke; upper limb; vagus nerve stimulation; Vivistim.

Keystone First- CHIP has developed clinical policies to assist with making coverage determinations. Keystone First- CHIP's clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Keystone First- CHIP, on a case by case basis, when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Keystone First- CHIP's clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Keystone First- CHIP's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First- CHIP will update its clinical policies as necessary. Keystone First- CHIP's clinical policies are not guarantees of payment.

Coverage policy

Vagus nerve stimulation as an adjunct to rehabilitation in members with upper limb impairment after stroke is investigational/not clinically proven and, therefore, not medically necessary.

Limitations

No limitations were identified during the writing of this policy.

Alternative covered services

Guideline-directed stroke rehabilitation services.

Background

Stroke is a leading cause of serious long-term disability. In the United States, stroke occurs in an estimated 800,000 people annually, and approximately two-thirds survive and require rehabilitation. Upper limb impairment is a common consequence, resulting in paresis, abnormal muscle tone, sensory disturbances, and reduced coordination (Tsao, 2022). Up to 22% of patients experience shoulder pain associated with shoulder subluxation and motor weakness in the first year following stroke (Winstein, 2016).

Customized rehabilitation applies focused, repetitive practice to maximize residual function, level of independence, and quality of life. Recovery targets the surviving brain tissue with the goal of promoting neural

repair (National Institute of Neurological Disorders and Stroke, 2023). Treatments in stroke recovery are considered nonvascular, both pharmacological and nonpharmacological, and are initiated in the subacute to chronic phases (days to years) after stroke (Lin, 2018).

Conventional interventions used in stroke recovery include physical, occupational, and speech therapy. Electrical neurostimulation has been proposed as adjunctive treatment to enhance recovery. Novel invasive approaches, such as transcranial magnetic stimulation and deep brain stimulation, target post-stroke deficits such as motor, language, memory, and neglect (Lin, 2018). Transcutaneous electrical nerve stimulation and neuromuscular electrical stimulation have been studied for treating hemiplegic shoulder pain, albeit with limited success (Winstein, 2016).

Vagus nerve stimulation represents a novel, drug-free, adjunctive treatment in stroke recovery for regaining upper extremity motor function. Its mechanism of action is not completely understood, but preclinical research suggests it modulates irregular electrical activity in the brain, thereby enhancing brain plasticity (Lin, 2018).

The U.S. Food and Drug Administration (2021) has granted premarket approval to one implantable vagus nerve stimulator for commercial use as a breakthrough technology designation: The MicroTransponder® Vivistim® Paired VNS System (MicroTransponder, Inc., Austin, Texas). Vivistim consists of a pulse generator implanted in the pectoral region, a lead electrode attached to the left vagus nerve in the neck, a wireless transmitter, and software. Vivistim is indicated for stimulation of the vagus nerve during rehabilitation therapy to reduce upper extremity motor deficits and improve motor function in patients with chronic ischemic stroke and moderate to severe arm impairment.

No transcutaneous vagus nerve stimulators have been approved for this indication (U.S. Food and Drug Administration, 2024).

Findings

The American Heart Association/American Stroke Association guideline for stroke rehabilitation, which preceded device approval, acknowledge that most evidence supporting stroke rehabilitation interventions is mixed or incomplete. However, stroke rehabilitation interventions still may be reasonable to perform. It cited interventions for improving upper extremity function as an example, but did not mention vagus nerve stimulation specifically (Winstein, 2016).

The Department of Veterans Affairs and Department of Defense (2019) joint guideline recommended externally applied functional electrical stimulation, neuromuscular electrical stimulation, or transcutaneous electrical nerve stimulation as an adjunctive treatment to improve upper and lower extremity motor function. However, stimulation using indwelling electrodes required further study to assess the benefits and risks.

The evidence of the safety, feasibility, and efficacy of vagus nerve stimulation in stroke rehabilitation consists of two pilot studies (ClinicalTrials.gov identifier NCT01669161, Dawson, 2016, n = 20; ClinicalTrials.gov identifier NCT02243020, Dawson, 2020, Kimberley, 2018, both n = 17) and one pivotal study (ClinicalTrials.gov identifier NCT03131960, Dawson, 2021, n = 108) that served as the basis for regulatory approval. All were randomized controlled trials with low risk of bias, sponsored by the manufacturer, and conducted by the same investigator group.

The pivotal study was a randomized, triple blinded, sham-controlled, multisite trial (n = 108) that compared rehabilitation with vagus nerve stimulation to rehabilitation alone (Dawson, 2021; Vagus nerve stimulation paired with rehabilitation for upper limb motor function after ischaemic stroke trial [VNS-REHAB]). Participants were adults with unilateral supratentorial chronic ischemic stroke and moderate-to-severe upper-limb impairment. The

demographic breakdown of the trial participants were 65% male, 78% White, 17% Black, and a median age of 62 years. The average time since ischemic stroke was 3.2 ± 2.5 years. All had received at least nine months (32 to 35 visits) of upper limb rehabilitation prior to study enrollment. Outcomes were assessed at baseline and at days 1, 30, and 90 after in-clinic therapy.

The study protocol comprised in-clinic rehabilitation administered in three two-hour sessions per week for six weeks. The stimulation settings were 0.8mA, 30Hz frequency, 100ms pulse width with pulse train of 0.5 seconds across studies. Dawson (2021) and Kimberley (2018) extended the rehabilitation protocol to 90 days of additional prescribed home therapy followed by the control group crossing over to receive six weeks of in-clinic rehabilitation with active vagus nerve stimulation and outcome assessments at days 1, 7, 30, and 90 thereafter. Dawson (2020, 2021) continued unblinded follow-up for one year.

The primary outcome measure was the change in Fugl-Meyer Assessment-upper extremity scores from baseline to various time points both within groups and between groups. A clinically meaningful response was defined as a six-point or greater improvement in the Fugl-Meyer Assessment-upper extremity score. Other efficacy endpoints were changes in the Wolf Motor Function Test, Box and Block Test, Nine-Hole Peg Test, Stroke Impact Scale, Motor Activity Log, and quality of life scores.

Rehabilitation with vagus nerve stimulation provided a small, statistically significant, incremental functional improvement and reduced deficits over rehabilitation alone (Dawson, 2021). However, small improvements that are statistically significant may not translate into clinically meaningful benefit from the patient's perspective. Kwakkel (2021) notes that between-group differences of 2.5 to 3 points on Fugl-Meyer Assessment-upper extremity scores are not remarkable in participants with chronic stroke treated at similar intensities. The lack of robust between-group differences and within-group improvements on the primary efficacy endpoint supports the need for additional research to clarify the efficacy of vagus nerve stimulation as an adjunct therapy.

Pivotal study results

Device use was well-tolerated. A total of 334 adverse events were reported, but only five events were severe, and none were related to surgery or stimulation (Dawson, 2021). Forty-five participants (42%) reported adverse events possibly, probably, or definitely related to device implantation, and the most common adverse event was pain (22%). One participant had transient vocal cord paresis. Sixteen (14.8%) participants had their device explanted by study end, and in 14, the reason was to exit the study. Surgery-related adverse event rates associated with vagus nerve stimulator implantation were lower for participants with chronic stroke than for those with epilepsy and depression reported in other studies (Liu, 2022a).

For the primary endpoint, from baseline to day 1 after completion of in-clinic therapy, the mean Fugl-Meyer Assessment-Upper Extremity score increased by 5.0 points ± 4.4 in the active group and by 2.4 points ± 3.8 in the control group ($P = .0014$). For the secondary endpoint analyses, at 90 days after in-clinic therapy, there were significant between-group differences (reported as active versus control) in (Dawson, 2021):

- The clinically meaningful response rate (47% versus 25%, $P < .01$).
- Increases in the Wolf Motor Function Test score (0.46 ± 0.40 points versus 0.16 ± 0.30 points, $P < .0001$).
- Increases in the Fugl-Meyer Assessment-Upper Extremity score (5.8 ± 6.0 points versus 2.8 ± 5.2 points, $P < .008$).

Potentially significant improvements with Vivistim were also observed in quality of life measures. One serious adverse event due to surgery occurred and fully resolved within five weeks. Interim 90-day data (n = 66) suggest

durable improvements in motor recovery and quality of life. The control participants who then received Vivistim had responses similar to the original active group (Dawson, 2021).

Dawson (2023) compared changes in the Fugl-Meyer Assessment-Upper Extremity score on the first day and after completion of six weeks of in-clinic therapy based on the following characteristics: gender, age (≥ 62 years), time from stroke (> two years), severity at baseline, paretic side, country of enrollment (United States vs. United Kingdom), and presence of cortical involvement of the index infarction. The between group difference and adverse event rates were similar across all subgroups.

One systematic review identified these three trials and three other trials of transcutaneous devices. Vagus nerve stimulation could be a feasible and safe therapy for upper limb motor impairment, but additional research is needed to define efficacy (Xie, 2021).

In 2023, we added new analyses from the VHS-REHAB trial and five new systematic reviews/meta-analyses to the policy. No policy changes are warranted.

The new systematic reviews/meta-analyses included the same relatively few published randomized controlled trials of implanted and transcutaneous vagus nerve stimulators as adjunct treatment in post-stroke rehabilitation. Their results confirm previous findings that vagus nerve stimulation is safe and effective for improving upper limb sensorimotor function based on moderate certainty evidence. The impact on long-term outcomes, mental health, or activities of daily living remain unclear. Additional independent research enrolling patients with different stroke characteristics is needed to further clarify the clinical role of percutaneous and transcutaneous vagus nerve stimulators in post-stroke rehabilitation (Ananda, 2022; Gao, 2023; Liu, 2022b; Ramos-Castaneda, 2022 ; Zhao, 2022.

In 2024, we updated the references and added a systematic review and meta-analysis to the policy with no policy changes warranted. In 10 trials (n = 335) comparing vagus nerve stimulation (percutaneous and transcutaneous) plus rehabilitation to no or sham rehabilitation, vagus nerve stimulation was safe and effective for treating upper extremity motor dysfunction after a stroke. Subgroup analyses suggest noninvasive vagus nerve stimulation integrated with rehabilitation and vagus nerve stimulation delivered at lower frequencies (< 25 Hertz) may be more effective applications for the functional restoration of the upper extremities. However, the effects of heterogeneity of the intervention and stroke on outcomes, prognostic indicators, and the role of objective neurophysiological measures are unresolved issues. The authors called for high-quality studies with larger study populations and more comprehensive and thorough data to clarify clinical application (Wang, 2023).

References

On April 26, 2024, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “stroke rehabilitation (MeSH),” “vagus nerve stimulation (MeSH),” “vagus nerve stimulation,” and “stroke.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

6/2022: initial review date and clinical policy effective date: 7/2022

6/2023: Policy references updated.

6/2024: Policy references updated.