I. Policy

Use of baroreflex stimulation implanted devices is considered investigational as there is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

II. Product Variations

[N] = No product variation, policy applies as stated
[Y] = Standard product coverage varies from application of this policy, see below

[N] Capital Cares 4 Kids
[N] PPO
[N] HMO
[N] SeniorBlue HMO
[N] SeniorBlue PPO

[N] Indemnity
[N] SpecialCare
[N] POS
[N] FEP PPO

III. Description/Background

Baroreflex stimulation devices are used to provide baroreflex activation therapy® (BAT®) which refers to electrical stimulation of the baroreceptors in the carotid arteries by means of an implanted device. Activation of the baroreflex causes inhibition of the sympathetic nervous system, resulting in a variety of physiologic changes including slowed heart rate and decreased blood pressure. Use of baroreflex stimulation devices has therefore been proposed as a treatment
for hypertension that is resistant to standard medications, as well as related conditions that are associated with high sympathetic tone.

**Background**

The baroreceptors are pressure sensors contained within the walls of the carotid arteries. They are part of the autonomic nervous system that regulates basic physiologic functions such as heart rate and blood pressure (BP). When these receptors are stretched, as occurs with increases in blood pressure, the baroreflex is activated. Activation of the baroreflex sends signals to the brain, which responds by inhibiting sympathetic nervous system output and increasing parasympathetic nervous system output. The effect of this activation is to reduce heart rate and blood pressure, thereby helping to maintain homeostasis of the circulatory system.

**Resistant hypertension.** Hypertension is a widely prevalent condition, which is estimated to affect approximately 30% of the population in the United States. (1) It accounts for a high burden of morbidity related to strokes, ischemic heart disease, kidney disease, and peripheral arterial disease. Resistant hypertension is defined as elevated blood pressure despite treatment with at least 3 antihypertensive agents at optimal doses. Resistant hypertension is a relatively common condition, given the large number of individuals with hypertension. In large clinical trials of hypertension treatment, up to 20-30% of participants meet the definition for resistant hypertension, and in tertiary care hypertension clinics, the prevalence has been estimated to be 11-18%. (1) Resistant hypertension is associated with a higher risk for adverse outcomes such as stroke, myocardial infarction (MI), heart failure, and kidney failure.

There are a number of factors that may contribute to uncontrolled hypertension, and these should be considered and addressed in all patients with hypertension prior to labeling a patient as resistant. These include non-adherence to medications, excessive salt intake, inadequate doses of medications, excess alcohol intake, volume overload, drug-induced hypertension, and other forms of secondary hypertension. (2) Also, sometimes it is necessary to address comorbid conditions, i.e., obstructive sleep apnea, in order to adequately control BP.

Treatment for resistant hypertension is mainly intensified drug therapy, sometimes with the use of non-traditional antihypertensive medications such as spironolactone and/or minoxidil. However, control of resistant hypertension with additional medications is often challenging and can lead to high costs and frequent adverse effects of treatment. As a result, there is a large unmet need for additional treatments that can control resistant hypertension. Non-pharmacologic interventions for resistant hypertension include modulation of the baroreflex receptor, and/or radiofrequency denervation of the renal nerves.

**Baroreflex activation devices.** Devices that activate the baroreflex are implantable devices that provide electrical stimulation to the baroreceptors. At least one company has developed devices for this purpose; no baroreflex activation device has received approval or clearance from the U.S. Food and Drug Administration (FDA).
The Rheos® Hypertension system (CRVx™, Minneapolis, MN) consists of 3 components:

1) Implantable pulse generator, which controls and delivers the electrical energy. It is implanted subcutaneously beneath the collarbone by minimally invasive surgery.

2) Carotid sinus leads, which are thin wires with electrical contacts that are placed in contact with the carotid baroreceptors. They conduct the electrical energy from the pulse generator to the baroreceptors.

3) The programmer system, which is an external device that allows clinicians to turn the system on and off and regulate the electrical signal delivered to the baroreceptors.

CVRx™ has replaced the Rheos® system with a “second-generation” device called the Barostim neo™. The device consists of a unilateral electrode and lead that is attached to the carotid sinus and a pulse generator that is implanted subcutaneously in the chest wall. Programming is performed via radiofrequency telemetry using an external laptop computer and software.

Regulatory Status

There are no baroreflex activation therapy devices that have received U.S. FDA approval or clearance.

IV. RATIONALE

Literature Review

The literature review focused on identification of controlled trials, particularly randomized controlled trials (RCTs). RCTs are crucial in determining efficacy of this treatment due to the natural variability in blood pressure (BP), the heterogeneity of the patient populations with increased BP, and the presence of many potential confounders of outcome. Case series have limited utility for determining efficacy. They can be useful for demonstrating potential of the technique, for determining the rate of short- and long-term adverse effects of treatment, and to evaluate the durability of the treatment response.

Clinical question: Is baroreflex stimulation effective in lowering blood pressure in patients with resistant hypertension?

There was one published RCT, the Rheos® pivotal trial and results of this study were reported in 2011. (3) The trial was double-blind and included patients with resistant hypertension defined as at least 1 systolic blood pressure measurement of 160 mm Hg or more with diastolic blood pressure 80 mm Hg or more after at least 1 month of maximally tolerated medical therapy. A
total of 322 patients had the Rheos® system implanted, and 265 patients underwent randomization. Participants were randomized in a 2:1 fashion to the device turned on or off for a 6-month period. After 6 months, all patients had the device turned on. The primary efficacy endpoints were the percent of patients achieving at least 10 mm Hg decrease in systolic blood pressure (SBP) at the 6-month time point (acute efficacy) and the percent of patients who maintained their blood pressure (BP) response over the 6-12 month time period (sustained efficacy). Primary safety outcomes were defined thresholds for procedural safety (at least 82% of patients free from procedural adverse events at 30 days), therapy safety (not more than 15% excess treatment-related adverse events in experimental group), and device safety (at least 72% of patients free from procedural or therapy-related adverse events at 12 months).

At 6 months, 54% of patients in the stimulation group had an SBP decrease of 10 mm Hg or more, compared to 46% of patients in the control group (p=0.97), indicating that the primary acute efficacy outcome was not met. The primary sustained efficacy outcome was met, with 88% of patients who responded at 6 months maintaining a response at 12 months. A secondary efficacy outcome, the percent of patients reaching target SBP, did show a significant group difference. A total of 42% of the patients in the active treatment group reached a target SBP of 140 mm Hg, compared with 24% in the control group (p=0.005). For the primary procedural safety, the predefined threshold of 82% was not met. At 30 days, the percent of patients free of procedural adverse events was 74.8%. The primary safety endpoint of therapy safety was met, with a similar percent of patients free of treatment-related side effects at 6 months (91.7% vs. 89.3%, p<0.001 for non-inferiority). The primary safety endpoint of device safety was also met, with 87.2% of patients free of device-related adverse events at 12 months, exceeding the predefined threshold of 72%.

Patients who actively participated in the Rheos® pivotal trial continued to be followed after 12 months and additional data were reported in 2012 by Bakris and colleagues. (4) A total of 276 of the 322 implanted patients (86%) consented to long-term open-label follow-up. After a mean follow-up of 28 months, 244 of 276 (88%) were considered to be clinically significant responders. Response was defined as sustained achievement of the target systolic blood pressure (140 mm Hg or less, or 130 mm Hg or less for patients with diabetes or renal disease), or a reduction in systolic blood pressure of 20 mm Hg or more from device activation. Alternatively, patients could qualify as a responder if their implanted device was deactivated and if they had an increase in systolic blood pressure of at least 20 mm Hg in the 30 days after device deactivation. In the extension study, there was no comparison group.

The DEBut-HT trial (5) was a multicenter, single-arm feasibility study of the Rheos® BAT system published in 2010. This study enrolled 45 subjects, from 9 clinical centers in Europe, with resistant hypertension defined as a blood pressure of greater than 160/90 despite treatment with at least 3 antihypertensive drugs, including a diuretic. The planned follow-up period was 3 months, with a smaller number of patients followed for up to 2 years. In 37 patients completing the 3-month protocol, systolic office blood pressure (BP) was reduced by 21±4 mm Hg (p<0.0001) and diastolic BP was reduced by 12±2 mm Hg (p<0.001). There was a smaller
reduction in 24-hour ambulatory BP (n=26), with a decrease of 6±3 mm Hg in systolic BP (p=0.10) and a decrease of 4±2 mm Hg in diastolic BP (p=0.04). In 26 patients followed for 1 year, the declines in office BP were 30±6 mm Hg systolic (p<0.001) and 20±4 mm Hg diastolic (p<0.001). For ambulatory BP (n=15), the 1-year declines were 13±3 mm Hg systolic (p<0.001) and 8±2 mm Hg diastolic (p=0.001). A total of 7/42 patients (16.7%) experienced adverse events. Three patients required device removal due to infection; one patient experienced perioperative stroke; one patient experienced tongue paresis due to hypoglossal nerve injury; one patient had postoperative pulmonary edema; and one patient required reintervention for movement of the device.

Several other smaller feasibility studies have been reported. For example, Heusser et al. (6) treated 12 individuals who had treatment-resistant hypertension with the Rheos® system. The mean baseline BP was 193/94 mm Hg, and at 1 month following implantation, there were decreases in systolic BP of 32±10 mm Hg (p=0.01). The decrease in diastolic BP was not reported. Tordoir et al. (7) treated 21 patients with the Rheos® system and reported acute decreases in BP at 1 to 3 days post-implantation. The mean baseline BP was 189.6/110.7 mm Hg, with a reduction post-treatment of 28±22 mm Hg systolic, and 16±11 diastolic. Adverse events reported included infection necessitating removal (n=1), hypoglossal nerve injury (n=1), wound complications (n=3); intraoperative bradycardia (n=2); and pain (n=5).

In 2012, Hoppe et al. published the results of a series of patients treated with the Barostim Neo™. (8) Thirty patients from 7 centers in Europe and Canada with resistant hypertension were treated with this device and followed for a 6-month period. The mean baseline BP was 172/100. At 6 months, there was a decrease in BP of 26.0 mm Hg systolic and 12.4 mm Hg diastolic. The percent of patients achieving adequate BP control, defined as a systolic BP of 140 or less, was 43%. There were 3 perioperative complications, one device pocket hematoma, one wound complication, and one intermittent pain at the insertion site. One additional patient had longer term intermittent pain at the device site.

Summary

The use of baroreflex stimulation devices is a potential alternative treatment for resistant hypertension. Specific devices for baroreflex stimulation have been developed, but none have received FDA-approval for any indication. Small, uncontrolled feasibility studies report short-term reductions in blood pressure, together with adverse events such as infection, hypoglossal nerve injury, and wound complications. Results of an RCT comparing baroreflex stimulation with continued medical therapy were published in 2011. This trial met some efficacy endpoints but not others. There was not a significant increase in the percent of patients achieving at least a 10 mm Hg decrease in systolic blood pressure (SBP) at 6 months, but more patients in the treatment group did reach a target systolic BP of 140 mm Hg or less at 6 months. The trial met 2 of 3 predefined safety endpoints. Further research from RCTs is needed to determine whether baroreflex activation therapy is effective in reducing blood pressure for patients with resistant
hypertension. Because of limited evidence showing benefit, and the lack of FDA approval, this treatment is considered investigational.

**Practice Guidelines and Position Statements**

No relevant practice guidelines or position statements were identified.

**Medicare National Coverage**

No national coverage determination.

**Ongoing Clinical Trials**

A search of online site ClinicalTrials.Gov on July 9, 2013 revealed the following ongoing randomized, controlled trials of baroreflex stimulation therapy:

**CVRx Barostim Hypertension Pivotal Trial (NCT01679132)**: This RCT is evaluating the safety and efficacy of the Barostim Neo device in people with treatment-resistant hypertension. Resistant hypertension is defined as a systolic blood pressure of at least 160 mm Hg, despite a stable regimen of 4 or more maximally tolerated anti-hypertensive medications. Patients will be randomized to receive optimal medical management alone or optimal medical management plus baroreflex stimulation. Primary outcomes are reduction in systolic blood pressure at 6 months and adverse events. The expected enrollment is 310 patients and the estimated date of study completion is July 2015.

**Barostim Hope for Heart Failure (HOPE4HF) Study (NCT01720160)**: This RCT is evaluating the safety and efficacy of the Barostim Neo device in people with heart failure. Patients will be randomized to receive optimal medical management alone or optimal medical management plus baroreflex stimulation. Primary outcomes are improvements in heart failure metrics and system and procedure-related adverse events. The expected enrollment is 60 patients and the estimated date of study completion is December 2015.

**Barostim Neo System in the Treatment of Heart Failure (NCT01471860)**: This is an RCT comparing baroreflex stimulation with medical management in patients with symptomatic heart failure despite a stable pharmacologic regimen. The primary outcome measure is change in left ventricular (LV) ejection fraction after 6 months’ follow-up. The planned enrollment is for 150 participants, with an estimated completion date of November 2014.
V.  **Definitions**

N/A

VI.  **Benefit Variations**

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based on all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII.  **Disclaimer**

*Capital’s 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. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.*

VIII.  **Coding Information**

*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.*

**Investigational; therefore not covered:**

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<th>CPT Codes®</th>
<th>0266T</th>
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*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.*
IX. REFERENCES

X. **Policy History**

| MP 1.142 | CAC 11/26/13 New policy. BCBSA adopted. Baroreflex stimulation implanted devices are considered investigational. |

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