Deep Brain Stimulation

Policy # 00024
Original Effective Date: 08/25/2005
Current Effective Date: 09/19/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider unilateral deep brain stimulation (DBS) of the thalamus in patients with disabling, medically unresponsive tremor due to essential tremor (ET) or Parkinson's disease (PD) to be **eligible for coverage**.

Based on review of available data, the Company may consider bilateral deep brain stimulation (DBS) of the thalamus in patients with disabling, medically unresponsive tremor in both upper limbs due to essential tremor (ET) or Parkinson's disease (PD) to be **eligible for coverage**.

Patient Selection Criteria
Coverage eligibility will be considered for deep brain stimulation (DBS) of the thalamus when the following criteria are met:
Disabling, medically unresponsive tremor defined as:

- Tremor causing significant limitation in daily activities; and
- Inadequate control by maximal dosage of medication for at least three months before implant.

Based on review of available data, the Company may consider unilateral or bilateral deep brain stimulation (DBS) of the globus pallidus or subthalamic nucleus when patient selection criteria are met to be eligible for coverage.

Patient Selection Criteria
Coverage eligibility will be considered for unilateral or bilateral deep brain stimulation (DBS) of the globus pallidus or subthalamic nucleus when all of the following criteria are met:

- Parkinson disease and ALL of the following:
    - A good response to levodopa; AND
    - Motor complications not controlled by pharmacologic therapy; AND
    - One of the following:
        - A minimum score of 30 points on the motor portion of the Unified Parkinson Disease Rating Scale when the patient has been without medication for approximately 12 hours OR
        - Parkinson disease for at least 4 years

- Patients older than 7 years with chronic, intractable (drug-refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis).

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company may consider deep brain stimulation (DBS) to be **not medically necessary**** when the following contraindications are present:

- Patients who are not good surgical risks because of unstable medical problems or because of the presence of a cardiac pacemaker; or
- Patients who have medical conditions that require repeated magnetic resonance imaging (MRI); or
- Patients who have dementia that may interfere with the ability to cooperate; or
- Patients who have had botulinum toxin injections within the last six months.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers deep brain stimulation for other movement disorders, including but not limited to tardive dyskinesia, multiple sclerosis, and post-traumatic dyskinesia to be **investigational.***

Based on review of available data, the Company considers deep brain stimulation for the treatment of chronic cluster headaches to be **investigational.***

Based on review of available data, the Company considers deep brain stimulation for the treatment of other psychiatric or neurologic disorders, including but not limited to epilepsy, Tourette syndrome, depression, obsessive-compulsive disorder, anorexia nervosa, alcohol addiction, Alzheimer disease, and chronic pain, to be **investigational.***

Background/Overview

DEEP BRAIN STIMULATION
DBS involves the stereotactic placement of an electrode into the brain (ie, hypothalamus, thalamus, globus pallidus, or subthalamic nucleus). The electrode is initially attached to a temporary transcutaneous cable for short-term stimulation to validate treatment effectiveness. Several days later, the patient returns for permanent subcutaneous surgical implantation of the cable and a radiofrequency-coupled or battery-powered programmable stimulator. The electrode is typically implanted unilaterally on the side corresponding to the most severe symptoms. However, use of bilateral stimulation using 2 electrode arrays has also been investigated in patients with bilateral, severe symptoms. After implantation, noninvasive

programming of the neurostimulator can be adjusted to the patient's symptoms. This feature may be important for patients with PD, whose disease may progress over time, requiring different neurostimulation parameters. Setting the optimal neurostimulation parameters may involve the balance between optimal symptom control and appearance of adverse effects of neurostimulation, such as dysarthria, disequilibrium, or involuntary movements.

Essential Tremor and PD
DBS has been investigated as an alternative to permanent neuroablative procedures, such as thalamotomy and pallidotomy. DBS has been most thoroughly investigated as an alternative to thalamotomy for unilateral control of ET and tremor associated with PD. More recently, there has been research interest in the use of DBS of the globus pallidus or subthalamic nucleus as a treatment of other parkinsonian symptoms, such as rigidity, bradykinesia, and akinesia. Another common morbidity associated with PD is the occurrence of motor fluctuations, referred to as "on and off" phenomena, related to the maximum effectiveness of drugs (ie, "on" state) and the nadir response during drug troughs (ie, "off" state). In addition, levodopa, the most commonly used anti-Parkinson drug, may be associated with disabling drug-induced dyskinesias. Therefore, the optimal pharmacologic treatment of PD may involve a balance between optimal effects on PD symptoms and the appearance of drug-induced dyskinesias. The effect of DBS on both PD symptoms and drug-induced dyskinesias has also been studied.

Primary and Secondary Dystonia
DBS has also been investigated in patients with primary and secondary dystonia, defined as a neurologic movement disorder characterized by involuntary muscle contractions, which force certain parts of the body into abnormal, contorted, and painful movements or postures. Dystonia can be classified according to age of onset, bodily distribution of symptoms, and cause. Age of onset can occur during childhood or during adulthood. Dystonia can affect certain portions of the body (focal dystonia and multifocal dystonia) or the entire body (generalized dystonia). Torticollis is an example of a focal dystonia. Primary dystonia is defined when dystonia is the only symptom unassociated with other pathology. Treatment options for dystonia include oral or injectable medications (ie, botulinum toxin) and destructive surgical or neurosurgical interventions (ie, thalamotomies or pallidotomies) when conservative therapies fail. Secondary dystonia is a dystonia brought on by an inciting event, such as a stroke, trauma, or drugs. Tardive dystonia is a form of drug-induced secondary dystonia.

Cluster Headaches
DBS has been investigated in patients with chronic cluster headaches. Cluster headaches occur as episodic attacks of severe pain lasting from 30 minutes to several hours. The pain is usually unilateral and localized to the eye, temple, forehead, and side of the face. Autonomic symptoms that occur with cluster headaches include ipsilateral facial sweating, flushing, tearing, and rhinorrhea. Cluster headaches occur primarily in men and have been classified as vascular headaches associated with high blood pressure, smoking, alcohol use, etc. However, the exact pathogenesis of cluster headaches is uncertain. Positron emission tomography scanning and magnetic resonance imaging have shown the hypothalamic region may

be important in the pathogenesis of cluster headaches. Alterations in hormonal or serotonergic function may also play a role. Treatment of cluster headaches includes pharmacologic interventions for acute episodes and prophylaxis, sphenopalatine ganglion (SPG) blockade, and surgical procedures such as percutaneous SPG radiofrequency rhizotomy, and gamma knife radiosurgery of the trigeminal nerve.

Neurologic and Psychiatric Disorders
The role of DBS in treatment of other treatment-resistant neurologic and psychiatric disorders, particularly epilepsy, Tourette syndrome, major depressive disorders, and obsessive-compulsive disorder, is also being investigated. Ablative procedures are irreversible and, though they have been refined, remain controversial treatments for intractable illness. Interest has shifted to neuromodulation through DBS of nodes or targets within neural circuits involved in these disorders. Currently, a variety of target areas are being studied.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
In 1997, the Activa®‡ Tremor Control System (Medtronic) was cleared for marketing by the U.S. FDA for deep brain stimulation. The Activa Tremor Control System consists of an implantable neurostimulator, a deep brain stimulator lead, an extension that connects the lead to the power source, a console programmer, a software cartridge to set electrical parameters for stimulation, and a patient control magnet, which allows the patient to turn the neurostimulator on and off, or change between high and low settings.

The original FDA-labeled indications for Activa were limited to unilateral implantation of the device for the treatment of tremor, but, in 2002, FDA-labeled indications were expanded to include bilateral implantation as a treatment to decrease the symptoms of advanced Parkinson disease not controlled by medication. In 2003, the labeled indications were further expanded to include "…unilateral or bilateral stimulation of the internal globus pallidus or subthalamic nucleus to aid in the management of chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis) in patients seven years of age or above." This latter indication was cleared for marketing by FDA through the humanitarian device exemption (HDE) process. In 2017, the indications for Parkinson disease were modified to include "adjunctive therapy in reducing some of the symptoms in individuals with levodopa-responsive Parkinson's Disease of at least 4 years' duration that are not adequately controlled with medication."

In 2009, the Reclaim®‡ device (Medtronic), a deep brain stimulator, was cleared for marketing by FDA through the HDE process for the treatment of severe obsessive-compulsive disorder.

In 2014, the Brio Neurostimulation System (now called Infinity; St. Jude Medical Neuromodulation) was cleared for marketing by FDA for the treatment of Parkinsonian tremor.

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In 2016, the St. Jude Medical's Infinity DBS device with directional leads was approved by FDA. The directional leads enable the clinician to "steer" current to different parts of the brain. This tailored treatment reduces side effects. The Infinity system can be linked to Apple's iPod Touch and iPad Mini.

In December 2017, a second system with directional leads, the Vercise Deep Brain Stimulation System (Boston Scientific), was approved by FDA. This system is to be used as an adjunctive therapy from reducing motor symptoms of moderate-to-advanced levodopa-responsive PD inadequately controlled with medication alone.

FDA product code: MHY.

Centers for Medicare and Medicaid Services (CMS)
Effective for services furnished on or after April 1, 2003, Medicare covers unilateral or bilateral thalamic ventralis intermedius nucleus (VIM) DBS for the treatment of ET and/or parkinsonian tremor and unilateral or bilateral STN or globus pallidus interna (GPi) DBS for the treatment of PD when the following conditions are met.

1. DBS devices must be FDA-approved devices for "DBS or devices used in accordance with FDA-approved protocols governing Category B Investigational Device Exemption (IDE) DBS clinical trials."
2. For thalamic VIM DBS, patients must meet all of the following criteria:
    a. "Diagnosis of ET based on postural or kinetic tremors of hand(s) without other neurologic signs, or diagnosis of idiopathic PD (presence of at least 2 cardinal PD features (tremor, rigidity or bradykinesia)) which is of a tremor-dominant form.
    b. Marked disabling tremor of at least level 3 or 4 on the Fahn-Tolosa-Marin Clinical Tremor Rating Scale (or equivalent scale) in the extremity intended for treatment, causing significant limitation in daily activities despite optimal medical therapy.
    c. Willingness and ability to cooperate during conscious operative procedure, as well as during postsurgical evaluations, adjustments of medications and stimulator settings."
3. For STN or GPi DBS, patients must meet all of the following criteria:
    a. "Diagnosis of PD based on the presence of at least 2 cardinal PD features (tremor, rigidity or bradykinesia).
    b. Advanced idiopathic PD as determined by the use of Hoehn and Yahr stage or Unified Parkinson's Disease Rating Scale (UPDRS) part III motor subscale.
    c. L-dopa responsive with clearly defined 'on' periods.
    d. Persistent disabling Parkinson's symptoms or drug side effects (eg, dyskinesias, motor fluctuations, or disabling 'off' periods) despite optimal medical therapy.
    e. Willingness and ability to cooperate during conscious operative procedure, as well as during post-surgical evaluations, adjustments of medications and stimulator settings."

DBS is not is not covered for ET or PD patients with any of the following:

1. "Non-idiopathic Parkinson's disease or 'Parkinson's Plus' syndromes.
2. Cognitive impairment, dementia or depression, which would be worsened by or would interfere with the patient's ability to benefit from DBS.
3. Current psychosis, alcohol abuse or other drug abuse.

Structural lesions such as basal ganglionic stroke, tumor or vascular malformation as etiology of the movement disorder.

Previous movement disorder surgery within the affected basal ganglion.

Significant medical, surgical, neurologic or orthopedic co-morbidities contraindicating DBS surgery or stimulation."

Rationale/Source

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 patients 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 one 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. RCTs 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.

ESSENTIAL TREMOR AND TREMOR IN PARKINSON DISEASE

Unilateral Stimulation of the Thalamus

This section was originally informed by a 1997 TEC Assessment that focused on unilateral DBS of the thalamus as a treatment of tremor. The Assessment concluded:

- Tremor suppression was total or clinically significant in 82% to 91% of operated sides in 179 patients who underwent implantation of thalamic stimulation devices. Results were durable for up to 8 years, and adverse effects of stimulation were reported as mild and largely reversible.

- These results were at least as good as those associated with thalamotomy. An additional benefit of DBS is that recurrence of tremor may be managed by changes in stimulation parameters.

Studies identified in subsequent literature searches have supported the conclusions of the TEC Assessment. For example, in 2008, Schuurman et al reported 5-year follow-up of 68 patients comparing thalamic stimulation with thalamotomy for treatment of tremor due to Parkinson disease (PD; 45 patients), essential tremor (ET; 13 patients), and multiple sclerosis (MS; 10 patients). Forty-eight (71%) patients were assessed at 5 years: 32 with PD, 10 with ET, and 6 with MS. The Frenchay Activities Index (FAI), the primary study outcome measure, was used to assess change in functional status; secondary measures included tremor severity, complication frequency, and patient-assessed outcomes. The mean difference (MD) between interventions, as measured on the FAI, favored thalamic stimulation at all time points: 4.4 (95% confidence interval [CI], 1.1 to 7.7) at 6 months, 3.3 (95% CI, -0.03 to 6.6) at 2 years, and 4.0 (95% CI, 0.3 to 7.7) at 5 years. The procedures had similar efficacy for suppressing tremors. The effect of thalamic stimulation diminished in half of the patients with ET and MS. Neurologic adverse effects were higher after thalamotomy. Subjective assessments favored stimulation.

Hariz et al (2008) evaluated outcomes of thalamic DBS in patients with tremor-predominant PD who participated in a multicenter European study and reported that, at 6 years postsurgery, tremor was still effectively controlled and appendicular rigidity and akinesia remained stable when compared with baseline.

Bilateral Stimulation of the Thalamus
In 2005, Putzke et al reported on a series of 25 patients with ET treated with bilateral DBS for management of midline tremor (head, voice, tongue, trunk). Three patients died of unrelated causes, 1 patient was lost to follow-up due to transfer of care, and 1 patient did not have baseline evaluation; these patients were not included in the analysis. Patients were evaluated at baseline (before implantation of second stimulator), and at 1, 3, 6, 12, 24, and 36 months. At 12 months, evaluations were obtained from 76% of patients; at 36 months, 50% of patients were evaluated. The most consistent improvement on the Tremor Rating Scale during both unilateral and bilateral stimulation was found for head and voice tremor. The incremental improvement over unilateral stimulation through the first 12 months of bilateral stimulation was significant ($p<0.01$). For bilateral stimulation at months 3 and 12, outcome measures were significantly better than unilateral stimulation at month 3 ($p<0.05$). Small sample size limited analysis at months 24 and 36. Dysarthria was reported in 6 (27%) patients and disequilibrium in 5 patients after bilateral stimulation in staged implantations. No patient reported dysarthria and 2 reported disequilibrium before bilateral stimulation.

In 2006, Pahwa et al reported on long-term follow-up of 45 patients who underwent thalamic DBS, 26 of whom had ET; of these patients, 18 had unilateral and 8 had bilateral implantation. Sixteen patients with unilateral and 7 with bilateral stimulators completed at least part of the 5-year follow-up evaluations. Patients with bilateral stimulation had a 78% improvement in mean motor tremor scores in the stimulation on state compared with baseline at 5-year follow-up ($p=0.02$) and 36% improvement in activities of daily

living (ADL) scores. Patients with unilateral stimulation improved 46% on motor tremor scores and 51% on ADLs ($p<0.01$). Stimulation-related adverse events were reported in more than 10% of patients with unilateral and bilateral thalamic stimulators. Most were mild and were reduced with changes in stimulation parameters. Adverse events in patients with bilateral stimulation (eg, dysarthria and other speech difficulties, disequilibrium or balance difficulties, abnormal gait) persisted, despite optimization of the stimulation parameters.

Directional Deep Brain Stimulation
Two new DBS systems with directional leads are currently available (approved by the FDA in 2016 and 2017). Directional leads potentially enable clinicians to target more specific areas of the brain to be treated with the direct current. Published evidence consists of several small observational studies, with sample sizes ranging from 7 to 13. The studies showed that patients experienced improved tremor scores and improved quality of life (QOL). Compared with historical data from conventional DBS systems, directional DBS widened the therapeutic window and achieved beneficial effects using lower current level. Comparative, larger studies are needed to support the conclusions from these small studies. Data from a large study of 292 patients are expected in 2018.

Section Summary: Essential Tremor and Tremor in Parkinson Disease
A TEC Assessment concluded there was sufficient evidence that DBS of the thalamus results in clinically significant tremor suppression and that outcomes after DBS were at least as good as thalamotomy. Subsequent studies reporting long-term follow-up have supported the conclusions of the Assessment and found that tremors were effectively controlled 5 to 6 years after DBS.

SYMPTOMS ASSOCIATED WITH PARKINSON DISEASE
Advanced Parkinson Disease

Stimulation of the Internal Segment of the Globus Pallidus Interna and Subthalamic Nucleus
This section was informed by a 2001 TEC Assessment that focused on the use of DBS of the internal segment of the GPi and subthalamic nucleus (STN) for a broader range of PD symptoms. The Assessment concluded:

- A wide variety of studies have consistently demonstrated that DBS of the GPi or STN results in significant improvements, as measured by standardized rating scales of neurologic function. The most frequently observed improvements consist of increased waking hours spent in a state of mobility without dyskinesia, improved motor function during “off” periods when levodopa is not effective, reduction in frequency and severity of levodopa-induced dyskinesia during periods when levodopa is working (“on” periods), improvement in cardinal symptoms of PD during periods when medication is not working, and, in the case of bilateral DBS of the STN, reduction in the required daily dosage of levodopa and/or its equivalents. The magnitude of these changes were both statistically significant and clinically meaningful.

- The beneficial treatment effect lasted at least for the 6 to 12 months observed in most trials. While there was not a great deal of long-term follow-up, the available data were generally positive.
- Adverse effects and morbidity were similar to those known to occur with thalamic stimulation.
- DBS possesses advantages to other treatment options. Compared to pallidotomy, DBS can be performed bilaterally. The procedure is nonablative and reversible.

A 2014 systematic review of RCTs by Perestelo-Perez et al compared the impact of DBS plus medication to medication alone (or plus sham DBS) on PD outcomes. Six RCTs (total N=1184 patients) were included in the review. Five trials exclusively involved bilateral stimulation to the STN and, in the sixth trial, half of the patients received stimulation to the STN and the other half had stimulation to the GPi. Motor function assessment was blinded in 2 trials and randomization method was described in 4 trials. Five studies reported motor function, measured by the UPDRS. In the off-medication phase, motor function was significantly higher with DBS than with control (weighted mean difference [WMD], 15.20; 95% CI, 12.23 to 18.18; standard mean difference [SMD], 1.35). In the on-medication phase, there was also significantly greater motor function with DBS than with control (WMD=4.36; 95% CI, 2.80 to 5.92; SMD=0.53). Meta-analyses of other outcomes (eg, ADLs, QOL, dementia, depression) also favored the DBS group.

An earlier (2006) systematic review included both RCTs and observational studies; reviewers examined the literature on subthalamic stimulation for patients with PD who had failed medical management. Twenty studies, primarily uncontrolled cohorts or case series, were included in the meta-analysis. Subthalamic stimulation was found to improve ADLs by 50% over baseline, as measured by the UPDRS-II (decrease of 13.35 points out of 52). There was a 28-point decrease in the UPDRS-III score (out of 108), indicating a 52% reduction in the severity of motor symptoms that occurred while the patient was not taking medication. A strong relation was found between the preoperative dose response to levodopa and improvements in both the UPDRS-II and -III scores. The analysis found a 56% reduction in medication use, a 69% reduction in dyskinesia, and a 35% improvement in QOL with subthalamic stimulation.

In 2007, a meta-analysis by Appleby et al found that the rate of suicidal ideation/suicide attempts associated with DBS for PD ranged from 0.3% to 0.7%. The completed suicide rate ranged from 0.16% to 0.32%. In light of the rate of suicide in patients treated with DBS, reviewers argued for prescreening for suicide risk.

Parkinson Disease With Early Motor Complications
In 2013, Schuepbach et al published an RCT evaluating DBS in patients with PD and early motor complications. Key eligibility criteria included age 18 to 60 years, disease duration of at least 4 year, improvement of motor signs of at least 50% with dopaminergic medication, and PD disease severity below stage 3 in the on-medication condition. At total of 251 patients enrolled, 124 of whom were assigned to DBS plus medical therapy and 127 to medical therapy alone. Analysis was intention to treat and blinded outcome assessment was done at baseline and 2 years.

The primary end point was mean change from baseline to 2 years in the summary index of the Parkinson Disease Questionnaire (PDQ-39), which has a maximum score is 39 points, with higher scores indicating higher QOL. Mean baseline scores on the PDQ-39 were 30.2 (SD=1.3) in the DBS plus medical therapy group and 30.2 (SD=1.2) in the medical therapy only group. At 2 years, the mean score increased by 7.8 points (SD=1.2) in the DBS plus medical therapy group and decreased by 0.2 points (SD=1.1) in the medical therapy only group. There was a significant difference between groups in the mean change, 8.0 (SD=1.6) (p=0.002). There were also significant between-group differences in major secondary outcomes, favoring the DBS plus medical therapy group (p<0.01 on each). These outcomes included severity of motor signs, ADLs, severity of treatment-related complications, and the number of hours with good mobility and no troublesome dyskinesia. The first 3 secondary outcomes were assessed using UPDRS subscales. Regarding medication use, the levodopa-equivalent daily dose was reduced by 39% in the DBS plus medical therapy group and increased by 21% in the medical therapy only group.

Sixty-eight patients in the DBS plus medical therapy group and 56 in the medical therapy only group experienced at least 1 serious adverse event (SAE). This included 26 SAEs in the DBS group that were surgery- or device-related; reoperation was necessary in 4 patients.

GPi vs STN Stimulation

A number of meta-analyses have compared the efficacy of GPi and STN stimulation in PD patients. One 2016 meta-analysis included only RCTs comparing the 2 types of stimulation in patients with advanced PD and considered a range of outcomes. This review, by Tan et al (2016), included RCTs evaluating patients with PD who were responsive to levodopa, had at least 6 months of follow-up, and reported at least 1 of the following outcome measures: UPDRS-III, Beck Depression Inventory–II (BDI), levodopa-adjusted dose (LED), neurocognitive status, or QOL. Ten RCTs met eligibility criteria and were included in the quantitative synthesis. After 6 months, there were no significant differences in the UPDRS-III scores between the GPi and STN groups for patients in the off-medication/on-simulation state (5 studies; MD = -1.39; 95% CI, -3.70 to 0.92) or the on-medication/on-stimulation state (5 studies; MD = -0.37; 95% CI, -2.48 to 1.73). At the 12- and 24-month follow-up, only 1 to 3 studies reported data on the UPDRS-III score. A pooled analysis of LED, there was a significant difference between the GPi and STN groups, favoring STN (6 studies; MD=0.60; 95% CI, 0.46 to 0.74). However, the analysis of BDI-II scores favored the GPI group (4 studies; MD = -0.31; 95% CI, -0.51 to -0.12). Other meta-analyses had similar mixed findings and none concluded that 1 type of stimulation was clearly better than the other for patients with advanced PD.

Section Summary: Symptoms Associated With Parkinson Disease

A number of RCTs and systematic reviews of the literature have been published. A TEC Assessment concluded that studies on DBS of the GPi or STN have consistently demonstrated clinically significant improvements in outcomes (eg, neurologic function). Other systematic reviews have also found significantly better outcomes after DBS than with a control intervention. One RCT compared the addition of DBS to medical therapy with medical therapy alone in patients with levodopa-responsive PD of at least 4 years in duration and uncontrolled motor symptoms. The trial found that that QOL at 2 years (eg, motor disability,

motor complications) was significantly higher when DBS was added to medical therapy. Meta-analyses of RCTs comparing GPi and STN have had mixed findings and did not show that 1 type of stimulation was clearly superior to the other.

PRIMARY DYSTONIA

DBS for the treatment of primary dystonia received U.S. FDA approval through the HDE process in 2003. The HDE approval process is available for conditions that affect fewer than 4000 Americans per year. According to this approval process, the manufacturer is not required to provide definitive evidence of efficacy, but only probable benefit. The approval was based on the results of DBS in 201 patients represented in 34 manuscripts. Three studies reported at least 10 cases of primary dystonia. In these studies, clinical improvement with DBS ranged from 50% to 88%. A total of 21 pediatric patients were studied; 81% were older than age 7 years. Among these patients, there was a 60% improvement in clinical scores. As noted in the analysis of risk and probable benefit, the only other treatment options for chronic refractory primary dystonia are neurodestructive procedures. DBS provides a reversible alternative.

In 2017, Moro et al published a systematic review of literature published through November 2015 on primary dystonia (also known as isolated dystonia). Reviewers included studies with at least 10 cases. Fifty-eight articles corresponding to 54 unique studies were identified; most involved bilateral DBS of the GPi. There were only 2 controlled studies, 1 RCT (Volkmann et al; described below) and 1 study that included a double-blind evaluation with and without stimulation. Twenty-four studies reported data using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) and were included in a meta-analysis. These studies enrolled a total of 523 patients (mean per study, 22 patients) and had a mean follow-up of 32.3 months (range, 6-72 months). In a pooled analysis of BFMDRS motor scores (scale range, 0-120; higher scores indicate more severe dystonia) from 24 studies, the mean increase in scores at 6 months compared with baseline was 23.8 points (95% CI, 18.5 to 29.1 points). The mean increase in the motor score at last follow-up compared with baseline was 26.6 points (95% CI, 22.4 to 30.9 points). The mean percentage improvement was 59% at 6 months and 65% at last follow-up. Fourteen studies reported BFMDRS disability scores (scale range, 0-30). Compared with baseline, the mean absolute change in the score was 4.8 points (95% CI, 3.1 to 6.6 points) at 6 months and 6.4 points (95% CI, 5.0 to 7.8 points) at last follow-up. The mean percentage improvement was 44% at 6 months and 59% at last follow-up.

The RCT, which was an industry-sponsored, patient- and observer-blinded evaluation of pallidal neurostimulation in subjects with refractory cervical dystonia, was published by Volkmann et al in 2014. The trial included 62 adults with cervical dystonia of at least 3 years in duration, a severity score of at least 15 on the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), and an unsatisfactory response to botulinum toxin injection and oral medication. Patients were randomized to DBS (n=32) or to sham stimulation (n=30). The primary outcome was change in the TWSTRS severity score at the end of the blinded study period (3 months); thereafter, all patients received open-label active stimulation. After 3 months, mean TWSTRS score improved by 5.1 points (95% CI, 3.5 to 7.0 points) in the neurostimulation group and by 1.3 points (95% CI, 0.4 to 2.2 points) in the sham group. The between-group difference was

3.8 points (95% CI, 1.8 to 5.8 points; p=0.024). Findings were mixed on the prespecified secondary outcomes. There was significantly greater improvement in the neurostimulation than in the sham group on the TWSTRS disability score and the Bain Tremor Scale score, but not on the TWSTRS pain score or the Craniocervical Dystonia Questionnaire–24 score. During the 3-month blinded study period, 22 adverse events were reported in 20 (63%) patients in the neurostimulation group and 13 adverse events were reported in 12 (40%) patients in the sham group. Of these 35 adverse events, 11 (31%) were serious. Additionally, 40 adverse events, 5 of which were serious, occurred during 9 months of the open-label extension period. During the study, 7 patients experienced dysarthria (ie, slightly slurred speech), which was not reversible in 6 patients.

Section Summary: Primary Dystonia
A review prepared for FDA and a 2017 systematic review have evaluated literature on DBS for primary dystonia. There are numerous small case series and 1 RCT. The RCT found that severity scores improved more after active than after sham stimulation. A pooled analysis of 24 studies, mainly uncontrolled, found improvements in motor scores and disability scores after 6 months and at last follow-up (mean, 32 months).

TARDIVE DYSKINESIA AND TARDIVE DYSTONIA
Stimulation of the GPi was examined as a treatment for tardive dyskinesia in a 2007 multicenter case series, with a double-blind evaluation at 6 months (comparison of symptoms in the on and off positions). The trial was stopped early due to successful treatment (>40% improvement at 6 months) in the first 10 patients. In the double-blind evaluation of these patients, stimulation was associated with a mean decrease of 50% in the symptom score when the device was on versus off.

Outcomes on motor function, QOL, and mood in a series 9 patients treated with DBS of the GPi for tardive dystonia were reported by Gruber et al in 2009. One week and 3 to 6 months after surgery, BFMDRS motor scores were improved by 56.4% and 74.1%, BFMDRS disability scores by 62.5% and 88.9%, and Abnormal Involuntary Movement Scale (AIMS) scores by 52.3% and 69.5%, respectively. At last follow-up (mean, 41 months; range, 18-90 months), BFMDRS motor scores were reduced compared with presurgical assessment by 83%, BFMDRS disability score by 67.7%, and AIMS scores by 78.7%.

Pouclet-Courtemanche et al (2016) reported on a case series of 19 patients with severe pharmaco-resistant tardive dyskinesia treated with DBS. Patients were assessed after 3, 6, and 12 months after the procedure. At 6 months, all patients had experienced greater than 40% reduction in symptoms as measured on the Extrapyramidal Symptoms Rating Scale (ESRS). At 12 months, the mean decrease in ESRS score was 58% (range, 21%-81%).

Section Summary: Tardive Dyskinesia and Tardive Dystonia
Evidence for the use of DBS to treat tardive syndromes consists of case series. One study of DBS in patients with tardive dyskinesia included a double-blind evaluation of DBS at 6 months. Symptoms decreased more with the device turned on but the study was small (10 patients were evaluated) and

included only patients with DBS for 6 months. Two subsequent case series included 9 and 19 patients, respectively, and reported favorable results with DBS treatment. Additional studies evaluating more patients, especially RCTs or other controlled studies, are needed to provide greater certainty concerning the efficacy of DBS for this population.

EPILEPSY

Systematic Reviews

Two systematic reviews on the use of DBS for drug-resistant epilepsy, both published in 2018, assessed many of the same studies. The larger review, by Li et al (2018), identified 10 RCTs and 48 uncontrolled studies. The literature search date was not reported. Meta-analyses were not performed. Summaries of the studies were discussed by area of the brain targeted by DBS. A review of the studies showed that DBS might be effective in reducing seizures when DBS targets the anterior nucleus of the thalamus or the hippocampus. Across studies, more than 70% of patients experienced a reduction in seizures by 50% or more. However, there were very few RCTs and the observational studies had small sample sizes. Individual responses varied, depending on seizure syndrome, presence or absence of structural abnormalities, and electrode position. Results were inconclusive when DBS targeted the centromedian nucleus of the thalamus, the cerebellum, and the subthalamic nuclei. Safety data on DBS were limited due to the small population sizes. The RCT in which DBS targeted the anterior nucleus of the thalamus (Fisher et al [2010] described below) reported paresthesias (23%), implant site pain (21%), and implant site infection (13%). Reviewers concluded that more robust clinical trials would be needed.

Randomized Controlled Trials

Fisher et al (2010) conducted a U.S. multicenter, double-blind, randomized trial, Stimulation of the Anterior Nuclei of the Thalamus for Epilepsy (SANTE) (see Table 1). Included were 110 patients, ages 18 to 65 years, who experienced at least 6 partial seizures (including secondarily generalized seizures) per month, but no more than 10 per day. (An additional 47 patients were enrolled in the trial but did not undergo implantation.) At least 3 antiepileptic drugs must have failed to produce adequate seizure control before baseline, with 1 to 4 antiepileptic drugs used at the time of study entry. Patients were asked to keep a daily seizure diary during treatment. All patients received DBS device implantation, with half the patients randomized to stimulation (n=54) and half to no stimulation (n=55) during a 3-month blinded phase; thereafter all patients received unblinded stimulation. Baseline monthly median seizure frequency was 19.5. During the first and second months of the blinded phase, the difference in seizure reduction between stimulation on (-42.1%) and stimulation off (-28.7%) did not differ significantly. In the last month of the blinded phase, the stimulated group had a significantly greater reduction in seizures (-40.4%) than the control group (-14.5%; p=0.002; see Table 2).

Troster et al (2017) assessed neuropsychological adverse events from the SANTE trial during the 3-month blinded phase, and at 7-year follow-up during the open-label noncomparative phase (see Table 2). At baseline, there were no differences in depression history between groups. During the 3-month blinded phase of the trial, depression was reported in 8 (15%) patients from the stimulation group and in 1 (2%)

patient from the no stimulation group (p=0.02). At 7-year follow-up, after the treatment groups had been combined, there was no statistically significant difference in Profile of Mood State depression score compared with baseline. Memory adverse events also occurred at significantly different rates between the treatment groups during the blinded phase (7 in the active group, 1 in the control group; p=0.03). At 7-year follow-up, most cognitive function tests did not improve over baseline measurements.

Cukiert et al (2017) conducted a double-blind, placebo-controlled randomized trial evaluating 16 patients with refractory temporal lobe epilepsy (see Table 1). All patients underwent DBS device implantation, and were followed for 6 months. Patients were seen weekly to receive the treatment or placebo. To maintain double-blind status, programming was performed by a nontreating assistant. Patients kept a seizure diary during the study period. Patients were considered seizure-free if no seizures occurred during the last 2 months of the trial. Responders were defined as patients experiencing a reduction of 50% or more in frequency reduction. Results are summarized in Table 2.

Table 1. Summary of RCT Characteristics for Epilepsy

Study	Country	Sites	Dates	Participants	Interventions	
					Active	Comparator
Fisher et al (2010); Troster et al (2017)	U.S.	17	NR	Patients with partial seizures, including secondary generalized seizures, refractory to ≥3 medications	5-V stimulus intensity (n=54)	No stimulation (n=55)
Cukiert et al (2017)	Brazil	1	2014-2016	Patients with temporal lobe epilepsy, refractory to ≥3 medications	Weekly 0.4-V to 2-V stimulus intensity (n=8)	Weekly impedance testing, no stimulation (n=8)

NR: not reported; RCT: randomized controlled trial; V: volts.

Table 2. Summary of RCT Outcomes for Epilepsy

Study	Seizure Reduction, % (p)			Adverse Events
	1 Month	2 Months	3 Months	
Fisher et al (2010); Troster et al (2017)				
Between-group difference	-11% (*NS*)	-11% (*NS*)	-29% (0.002)	3 months: higher rate of depression and memory adverse events in treatment group (difference disappeared in long-term follow-up)
FIAS at 6 Months				
Cukiert et al (2017)				
Stimulation on	4 seizure-free; 3 responders; 1 no response			2 patients with local skin erosions at cranial site of implant, treated with antibiotics
Stimulation off	0 seizure-free; 3 responders; 5 no response			

FIAS: focal impaired awareness seizure; RCT: randomized controlled trial.

Observational Studies

Long-term outcomes of the SANTE trial were reported by Salanova et al (2015). The uncontrolled open-label portion of the trial began after 3 months and, beginning at 13 months, stimulation parameters could be adjusted at the clinician's discretion. Of the 110 implanted patients, 105 (95%) completed the 13-month follow-up, 98 (89%) completed the 3-year follow-up, and 83 (75%) completed 5 years. Among patients with

at least 70 days of diary entries, the median change in seizure frequency from baseline was 41% at 1 year and 69% at 5 years ($p<0.001$ for both). During the trial, 39 (35%) of 110 patients had a device-related serious adverse event, most of which occurred in the first months after implantation. They included implant-site infection (10% of patients) and lead(s) not within target (8.2% of patients). Seven deaths occurred during the trial and none was considered to be device-related. Depression was reported in 41 (37%) patients following implant; in 3 cases, it was considered device-related. Memory impairment (nonserious) was reported in 30 (27%) patients during the trial, half of whom had a history of the condition. Although some patients appeared to benefit from treatment during the extended follow-up phase, the difference between groups in the blinded portion of the trial, while significant, was modest overall.

Kim et al (2017) conducted a retrospective chart review of 29 patients with refractory epilepsy treated with DBS. Patients' mean age was 31 years, they had had epilepsy for a mean of 19 years, and had a mean preoperative frequency of tonic-clonic seizures of 27 per month. Mean follow-up was 6.3 years. Median seizure reduction from baseline was 71% at year 1, 74% at year 2, and ranged from 62% to 80% through 11 years of follow-up. Complications included 1 symptomatic intracranial hemorrhage, 1 infection requiring removal and reimplantation, and 2 lead disconnections.

Section Summary: Epilepsy
A systematic review identified several RCTs and many observational studies in which DBS was evaluated for the treatment of epilepsy. The largest RCT consisted of a 3-month blinded phase in which patients were randomized to stimulation or no stimulation. After the randomized phase, all patients received stimulation and were followed for 13 additional months. Findings in the first 3 months were mixed: patients reported significantly fewer seizures in the third month, but not in the first or second month. In the uncontrolled follow-up period of the RCT and in many small observational studies, patients reported fewer seizures compared with baseline, however, without a control group, interpretation of results is limited. Adverse events, including device-related serious adverse events were reported in about one-third of patients. The risk-benefit ratio is uncertain.

MULTIPLE SCLEROSIS
Schuurman et al (2008) reported on 5-year follow-up for 68 patients in a study that compared thalamic stimulation with thalamotomy for multiple indications, including 10 patients with MS. Trial details are discussed with essential tremor in the section on Unilateral Stimulation of the Thalamus. The small numbers of patients with MS in this trial limits conclusions that can be drawn.

Section Summary: Multiple Sclerosis
One RCT reporting on 10 MS patients provides insufficient data for drawing conclusions on the efficacy of DBS for this population.

TOURETTE SYNDROME

Several systematic reviews of the literature on DBS for Tourette syndrome have been published. Most recent systematic reviews (ie, those published in 2015-2017) qualitatively described the literature. Only Baldermann et al (2016) conducted pooled analyses of study data. That review identified 57 studies on DBS for Tourette syndrome, four of which were randomized crossover studies. The studies included a total of 156 cases. Twenty-four studies included a single patient and 4 had sample sizes of 10 or more (maximum, 18 patients). Half of the patients (n=78) received thalamus stimulation and the next most common areas of stimulation were the GPi anteromedial part (n=44) and post ventrolateral part (n=20). Two of the RCTs used thalamic stimulation, one used bilateral globus pallidus stimulation, and one used both. The primary outcome was the Yale Global Tic Severity Scale (YGTSS). In a pooled analysis of within-subject pre-post data, there was a median improvement of 53% in YGTSS score, a decline from a median score of 83 to 35 at last follow-up. Moreover, 81% of patients showed at least a 25% reduction in YGTSS score and 54% showed improvements of 50% or more. In addition, data were pooled from the 4 crossover RCTs: 27 patients received DBS and 27 received a control intervention. Targets included the thalamus and the globus pallidus. In the pooled analysis, there was a statistically significant between-group difference, favoring DBS (SMD=0.96; 95% CI, 0.36 to 1.56). Reviewers noted that the effect size of 0.96 would be considered be large.

A systematic review by Piedad et al (2012) examined patient and target selection for use of DBS for subjects with Tourette syndrome. Most clinical trials evaluating DBS for Tourette syndrome have targeted the medial thalamus at the crosspoint of the centromedian nucleus, substantia periventricularis, and nucleus ventro-oralis internus. Other targets investigated have included the STN, caudate nucleus, GPi, and the anterior limb of the internal capsule and nucleus accumbens. Reviewers found no clear consensus in the literature for which patients should be treated and what the best target is.

The crossover RCT with the largest sample size was published by Kefalopoulou et al (2015). The double-blind trial included 15 patients with severe medically refractory Tourette syndrome; all received bilateral GPi surgery for DBS and were randomized to the off-stimulation phase first or the on-stimulation phase first for 3 months, followed by the opposite phase for the next 3 months. Of the 15 receiving surgery, 14 were randomized and 13 completed assessments after both on and off phases. For the 13 trial completers, mean YGTSS scores were 80.7 in the off-stimulation phase and 68.3 in the on-stimulation phase. The mean difference in YGTSS scores indicated an improvement of 12.4 points (95% CI, 0.1 to 24.7 points), which was statistically significant (p=0.048) after Bonferroni correction. There was no significant between-group difference in YGTSS scores for patients randomized to the on-stimulation phase first or second. Three serious adverse events were reported, 2 related to surgery and 1 related to stimulation. Reviewers noted that the most effective target of the brain for DBS in patients with Tourette syndrome needs additional study.

Section Summary: Tourette Syndrome
A number of uncontrolled studies,4 crossover RCTs, and several systematic reviews have been published. Most studies, including the RCTs, had small sample sizes (ie, ≤15 patients) and used a variety of DBS targets. A 2015 meta-analysis suggested that DBS might improve outcomes in patients with Tourette syndrome. However, the optimal target for DBS is not known and additional controlled studies in larger numbers of patients are needed.

CLUSTER HEADACHE AND FACIAL PAIN
DBS of the posterior hypothalamus for the treatment of chronic cluster headaches has been investigated, because functional studies have suggested cluster headaches have a central hypothalamic pathogenesis.

Fontaine et al (2010) published the results of a prospective crossover, double-blind, multicenter trial in 11 patients who received DBS of the posterior hypothalamus for severe refractory chronic cluster headache. The randomized phase compared active with sham stimulation during 1-month periods and was followed by a 1-year open phase. Severity of cluster headache was assessed using the weekly attack frequency (primary outcome), pain intensity, sumatriptan injections, emotional impact, and QOL (12-Item Short-Form Health Survey). During the randomized phase, no significant changes in primary or secondary outcome measures were observed between active and sham stimulation. At the end of the open phase, 6 of 11 patients reported greater than 50% reduction in the weekly frequency of attacks.

Another research group from Europe published 2 case series (potentially overlapping) on use of DBS for the ipsilateral posterior hypothalamus in patients with chronic cluster headache. Stimulation was reported to result in long-term pain relief (1-26 months of follow-up) without significant adverse events in 16 patients with chronic cluster headaches and in 1 patient with neuralgiform headache; treatment failed in the 3 patients who had atypical facial pain.

Section Summary: Cluster Headache and Facial Pain
Several case series and a crossover RCT have been published on use of DBS for cluster headache or facial pain. The RCT included 11 patients; there were no significant differences between groups receiving active and sham stimulation. Additional RCTs or controlled studies are needed.

TREATMENT-RESISTANT DEPRESSION
Systematic Reviews
A variety of target areas are being investigated for use of DBS for treatment-resistant depression. A systematic review by Morishita et al (2014) identified 22 published reports with 6 different approaches or targets, including the nucleus accumbens, ventral capsule/ventral striatum, subgenual cingulate cortex, lateral habenula, inferior thalamic nucleus, and medial forebrain bundle. Only 3 identified studies were controlled with sham stimulation periods, and 2 multicenter RCTs evaluating subgenual cingulate cortex and ventral striatum/ventral capsule DBS were terminated due to futility (interim analysis demonstrating

very low probability of success if the trial was completed as planned). A systematic review by Mosley et al (2015) identified an RCT on DBS for depression[44]; this trial is described next.

Randomized Controlled Trials

An industry-sponsored, double-blind RCT evaluating DBS targeting the ventral capsule/ventral striatum in patients with chronic treatment-resistant depression was published by Dougherty et al (2015). The trial included 30 patients with a major depressive episode lasting at least 2 years and inadequate response to at least 4 trials of antidepressant therapy. Participants were randomized to 16 weeks of active (n=16) or to sham (n=14) DBS, followed by an open-label continuation phase. One patient, who was assigned to active treatment, dropped out during the blinded treatment phase. The primary outcome was clinical response at 16 weeks, defined as 50% or more improvement from baseline on Montgomery-Asberg Depression Rating Scale (MADRS) score. A response was identified in 3 (20%) of 15 patients in the active treatment group and in 2 (14%) of 14 patients in the sham control group (p=0.53). During the blinded treatment phase, psychiatric adverse events occurring more frequently in the active treatment group included worsening depression, insomnia, irritability, suicidal ideation, hypomania, disinhibition, and mania. Psychiatric adverse events occurring more frequently in the sham control group were early morning awakening and purging. Findings of this trial did not support a conclusion that DBS is effective for treating treatment-resistant depression.

A crossover RCT evaluating active and sham phases of DBS stimulation in 25 patients with treatment-resistant depression was published after the systematic review by Bergfeld et al (2016). Prior to the randomized phase, all patients received 52 weeks of open-label DBS treatment with optimization of settings. Optimization ended when patients achieved a stable response of at least 4 weeks or after the 52-week period ended. At the end of the open-label phase, 10 (40%) patients were classified as responders (≥50% decrease in the Hamilton Depression Rating Scale [HAM-D] score) and 15 (60%) patients were classified as nonresponders. After the 52 weeks of open-label treatment, patients underwent 6 weeks of double-blind active and sham stimulation. Sixteen (64%) of 25 enrolled patients participated in the randomized phase (9 responders, 7 nonresponders). Nine patients were prematurely crossed over to the other intervention. Among all 16 randomized patients, HAM-D scores were significantly improved at the end of the active stimulation phase (mean HAM-D score, 16.5) compared with the sham stimulation phase (mean HAM-D score, 23.1; p<0.001). Mean HAM-D scores were similar after the active (19.0) and sham phases for initial nonresponders (23.0). Among initial responders, the mean HAM-D score was 9.4 after active stimulation and 23 after sham stimulation. Trial limitations included the small number of patients in the randomized phase and potential bias from having an initial year of open-label treatment; patients who had already responded to DBS over a year of treatment were those likely to respond to active than sham stimulation in the double-blind randomized phase; and findings might not be generalizable to patients with treatment-resistant depression who are DBS-naive.

Section Summary: Treatment-Resistant Depression
A number of case series and several RCTs evaluating DBS in patients with treatment-resistant depression have been published. Two RCTs were terminated for futility. Another RCT did not find a statistically significant difference between groups in the primary outcome (clinical response) and adverse psychiatric events occurred more frequently in the treatment group than in the control group. More recently, a controlled crossover trial randomized patients to active or to sham stimulation after a year of open-label stimulation. There was a greater reduction in symptom scores after active stimulation, but only in patients who were responders in the open-label phase; these findings might not be generalizable.

OBSESSIVE-COMPULSIVE DISORDER
Several systematic reviews evaluating DBS for obsessive-compulsive disorder (OCD) have been published. Two of these reviews included meta-analyses and pooled study findings. Kisely et al (2014) included only double-blind RCTs of active vs sham DBS. Five trials (total N=50 patients) met eligibility criteria and data on 44 patients were available for meta-analysis. Three were parallel-group RCTs with or without a crossover phase and 2 were only crossover trials. The site of stimulation was the anterior limb of the internal capsule (3 studies), the nucleus accumbens (1 study), and the STN (1 study). Duration of treatment ranged from 2 to 12 weeks. All studies reported scores on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), which is a 10-item clinician-rated scale, in which higher ratings reflect more intense symptoms, and a score of 24 or more (of a possible 40) indicates severe illness. Most studies designate a therapeutic response as a reduction in Y-BOCS score of 35% or more from the pretreatment baseline, with a reduction of 25% to 35% considered a partial response. Only 1 of the 5 studies compared the proportion of responders on the Y-BOCS as an outcome measure and that study did not find a statistically significant difference between active and sham stimulation groups. All studies reported the outcome measure, mean reduction in Y-BOCS score. When data from the 5 studies were pooled, there was a statistically significant reduction in the mean Y-BOCS in the active vs the sham group (MD = -8.49; 95% CI, -12.18 to -4.80). The outcome measure, however, does not permit conclusions on whether the between-group difference is clinically meaningful. Trial authors reported 16 serious adverse events including 1 cerebral hemorrhage and 2 infections requiring electrode removal. Additionally, nonserious transient adverse events were reported, including 13 reports of hypomania, 6 of increase in depressive or anxious symptoms, and 6 of headaches.

A meta-analysis by Alonso et al (2015) included studies of any type (including case reports) evaluating DBS for OCD and reporting changes in Y-BOCS score. Reviewers identified 31 studies (total N=116 patients). They did not report study type (ie, controlled vs uncontrolled); however, the meta-analysis only included patients who received active treatment. Twenty-four (77%) studies included 10 or fewer patients. Most studies (24, including 83 patients) involved DBS of striatal areas. Of the remaining studies, 5 (27 patients) addressed STN stimulation and 2 (6 patients) addressed stimulation of the inferior thalamic peduncle. Twelve studies provided patient-level data and 4 provided pooled data on percentage of responders (ie, >35% reduction in posttreatment Y-BOCS scores). Pooled analysis yielded a global percentage of responders of 60% (95% CI, 49% to 69%). The most frequent adverse events reported were worsening anxiety (25 patients) and hypomanic symptoms (23 patients). Reviewers reported on the benefits and risks

of DBS stimulation but could not draw conclusions about stimulation to any particular region or about the safety or efficacy of DBS for OCD compared with sham stimulation or other therapy.

Section Summary: Obsessive-Compulsive Disorder
The literature on DBS for OCD consists of several RCTs and a number of uncontrolled studies. Most studies had small sample sizes. Only 1 of the 5 RCTs identified in a 2015 meta-analysis reported the outcome measure of greatest interest—clinically significant change in Y-BOCS scores. Uncontrolled data have suggested improvements in OCD symptoms after DBS treatment, but have also identified a substantial number of adverse events. Additional blinded controlled studies are needed to draw conclusions about the impact of DBS on the net health benefit.

OTHER INDICATIONS
The evidence on use of DBS for anorexia nervosa, alcohol addiction, Alzheimer disease, Huntington disease, and chronic pain consists of small case series. These case series provide inadequate evidence on which to assess efficacy.

SUMMARY OF EVIDENCE
For individuals who have essential tremor or tremor in PD who receive DBS of the thalamus, the evidence includes a systematic review and case series. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. The systematic review (a TEC Assessment) concluded that there was sufficient evidence that DBS of the thalamus results in clinically significant tremor suppression and that outcomes after DBS were at least as good as thalamotomy. Subsequent studies reporting long-term follow-up have supported the conclusions of the TEC Assessment and found that tremors were effectively controlled 5 to 6 years after DBS. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have symptoms (eg, speech, motor fluctuations) associated with PD (advanced or >4 years in duration with early motor symptoms) who receive DBS of the GPi or STN, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. One of the systematic reviews (a TEC Assessment) concluded that studies evaluating DBS of the GPi or STN have consistently demonstrated clinically significant improvements in outcomes (eg, neurologic function). Other systematic reviews have also found significantly better outcomes after DBS than after a control intervention. An RCT in patients with levodopa-responsive PD of at least 4 years in duration and uncontrolled motor symptoms found that quality of life at 2 years was significantly higher when DBS was provided in addition to medical therapy. Meta-analyses of RCTs comparing DBS of the GPi with DBS of the STN have reported mixed findings and have not shown that 1 type of stimulation is clearly superior to the other. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have primary dystonia who receive DBS of the GPi or STN, the evidence includes systematic reviews, an RCT, and case series. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. A pooled analysis of 24 studies, mainly uncontrolled, found improvements in motor scores and disability scores after 6 months and at last follow-up (mean, 32 months). A double-blind RCT found that severity scores improved more after active than after sham stimulation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have tardive dyskinesia or tardive dystonia who receive DBS, the evidence includes case series, one of which included a double-blind comparison of outcomes when the DBS device was turned on versus off. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Few studies were identified and they had small sample sizes (range, 9-19 patients). Additional studies, especially RCTs or other controlled studies, are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have epilepsy who receive DBS, the evidence includes 2 systematic reviews of RCTs and many observational studies. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Two RCTs were identified. The larger reported that DBS had a positive impact during some parts of the blinded trial phase but not others, and a substantial number of adverse events (in >30% of patients). The smaller RCT (N=16) showed a benefit with DBS. Many small observational studies reported fewer seizures compared with baseline, however, without control groups, interpretation of these results is limited. Additional trials are required to determine the impact of DBS on patient outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have multiple sclerosis who receive DBS, the evidence includes an RCT. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. One RCT with 10 multiple sclerosis patients is insufficient evidence on which to draw conclusions about the efficacy of DBS in this population. Additional trials are required. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have Tourette syndrome who receive DBS, the evidence includes crossover RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Several small (≤15 patients) crossover trials and a 2015 meta-analysis have suggested that DBS may improve outcomes in patients with Tourette syndrome. However, the optimal target of the brain for DBS is unknown, so additional controlled studies in larger numbers of patients are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have cluster headaches or facial pain who receive DBS, the evidence includes a randomized crossover study and case series. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. In the randomized study, the between-group difference in

response rates did not differ significantly between active and sham stimulation phases. Additional RCTs or controlled studies are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have treatment-resistant depression who receive DBS, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. The only double-blind, parallel-group RCT in patients with depression did not find that DBS significantly increased the response rate compared with sham; 2 other RCTs were stopped due to futility. A crossover controlled trial randomized patients to active or to sham stimulation after a year of open-label stimulation. There was a greater reduction in symptom scores after active stimulation, but only in patients who were responders in the open-label phase; these findings might not be generalizable. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have obsessive-compulsive disorder who receive DBS, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Among the RCTs on DBS for obsessive-compulsive disorder, only one has reported the outcome of greatest clinical interest (therapeutic response rate), and that trial did not find a statistically significant benefit for DBS compared with sham treatment. The evidence is insufficient to determine the effects of the technology on health.

For individuals who have anorexia nervosa, alcohol addiction, Alzheimer disease, Huntington disease, or chronic pain who receive DBS, the evidence includes case series. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. RCTs are needed to evaluate the efficacy of DBS for these conditions. The evidence is insufficient to determine the effects of the technology on health outcomes.

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Policy History

Original Effective Date:	08/25/2005
Current Effective Date:	09/19/2018
03/21/2002	Medical Policy Committee review
03/25/2002	Managed Care Advisory Council approval
06/24/2002	Format revision. No substance change to policy.
08/03/2004	Medical Director review
08/17/2004	Medical Policy Committee review
08/30/2004	Managed Care Advisory Council approval
07/14/2005	Medical Director review
07/19/2005	Medical Policy Committee review. Clinical criteria revision. Coverage eligibility changes. Added investigational statement for DBS for cluster headaches.
08/24/2005	Managed Care Advisory Council approval
06/07/2006	Medical Director review
06/21/2006	Medical Policy Committee approval. Format revisions, FDA/Governmental, Rationale/Source. Coverage eligibility unchanged.

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08/01/2007	Medical Director review
08/15/2007	Medical Policy Committee approval. No change to coverage eligibility.
08/06/2008	Medical Director review
08/20/2008	Medical Policy Committee approval. Tardive dyskinesia, Tourette syndrome, depression and epilepsy were added to the list of investigational indications.
08/06/2009	Medical Policy Committee approval
08/26/2009	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/01/2010	Medical Policy Committee approval
07/21/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/07/2011	Medical Policy Committee approval
07/20/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/28/2012	Medical Policy Committee approval
07/27/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/04/2013	Coding Updated
06/27/2013	Medical Policy Committee approval
07/17/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/10/2014	Medical Policy Committee approval
07/16/2014	Medical Policy Implementation Committee approval. Added anorexia nervosa, alcohol addiction, and chronic pain as investigational indications
01/01/2015	Coding Updated
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
09/03/2015	Medical Policy Committee approval
09/23/2015	Medical Policy Implementation Committee approval. Added eligibility statement for bilateral DBS of thalamus for bilateral tremors and added Alzheimer disease to list of investigational indications
01/01/2016	Coding update
09/08/2016	Medical Policy Committee approval
09/21/2016	Medical Policy Implementation Committee approval. Added “upper” to coverage statement for bilateral DBS.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
09/07/2017	Medical Policy Committee approval
09/20/2017	Medical Policy Implementation Committee approval. In medically necessary statement on unilateral or bilateral deep brain stimulation of the globus pallidus or subthalamic nucleus, “OR Parkinson disease for at least 4 years” added to medically necessary criteria for use in Parkinson disease.
09/06/2018	Medical Policy Committee approval
09/19/2018	Medical Policy Implementation Committee approval. No change to coverage.

Next Scheduled Review Date: 09/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	61850, 61860, 61863, 61864, 61867, 61868, 61870, 61880, 61885, 61886, 95970, 95978, 95979
HCPCS	C1816, C1820, C1822, C1883, L8680, L8681, L8682, L8683, L8684, L8685, L8686, L8687, L8688, L8689
ICD-10 Diagnosis	F10.20, F32.89-F32.9, F34.81, F34.89, F50.00-F50.02, F95.2, G20, G21.11-G21.19, G21.2-G21.9, G24.01- G24.09, G24.1-G24.9, G25.0-G25.2, G35, G40.A01-G40.A09, G40.A11-G40.A19, G44.001-G44.009, G89.21-G89.29, G89.3-G89.4

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association TEC or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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