BlueCross BlueShield of Alabama

Name of Policy:

Deep Brain Stimulation

Policy #: 347
Category: Surgery

Latest Review Date: May 2018
Policy Grade: B

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *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.*

Proprietary Information of Blue Cross and Blue Shield of Alabama
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Description of Procedure or Service:

Deep brain stimulation (DBS) involves the stereotactic placement of an electrode into the brain (i.e., hypothalamus, thalamus, globus pallidus, or subthalamic nucleus). DBS is used as an alternative to permanent neuroablative procedures for control of essential tremor (ET) and Parkinson's disease (PD). DBS is also being evaluated for the treatment of a variety of other neurologic and psychiatric disorders.

Deep Brain Stimulation

DBS involves the stereotactic placement of an electrode into the brain (i.e., 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 to surgery for permanent subcutaneous 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, the use of bilateral stimulation using two 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 side effects of neurostimulation, such as dysarthria, disequilibrium, or involuntary movements.

Essential Tremor and PD

Deep brain stimulation has been investigated as an alternative to permanent neuroablative procedures, such as thalamotomy and pallidotomy. The technique has been most thoroughly investigated as an alternative to thalamotomy for unilateral control of essential tremor and tremor associated with Parkinson's disease. More recently, there has been research interest in the use of deep brain stimulation of the globus pallidus or subthalamic nucleus as a treatment of other parkinsonian symptoms, such as rigidity, bradykinesia, or 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 (i.e., the “on” state) and the nadir response during drug troughs (i.e., the “off” state). In addition, levodopa, the most commonly used anti-Parkinson's drug, may be associated with disabling drug-induced dyskinesias. Therefore, the optimal pharmacologic treatment of PD may involve a balance between optimal effects on Parkinson's symptoms versus the appearance of drug-induced dyskinesias. The effect of deep brain stimulation (DBS) on both Parkinson's 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 neurological 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 (i.e., botulinum toxin) and destructive surgical or neurosurgical interventions (i.e., 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 that have been associated with high blood pressure, smoking, alcohol use, etc. However, the exact pathogenesis of cluster headaches is uncertain. Positron emission tomography (PET) scanning and magnetic resonance imaging (MRI) have shown the hypothalamic region may be important in the pathogenesis of cluster headaches. Alterations in hormonal/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 Tourette syndrome, epilepsy, obsessive-compulsive and major depressive disorders 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.

Policy:

Effective for dates of service on or after November 13, 2014:

Unilateral deep brain stimulation of the thalamus meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage in patients with disabling, medically unresponsive tremor due to essential tremor or Parkinson's disease.

Disabling, medically unresponsive tremor is defined as all of the following:

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

Bilateral deep brain stimulation of the thalamus meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage in patients with disabling, medically unresponsive tremor in both upper limbs due to essential tremor or Parkinson disease.

Unilateral or bilateral deep brain stimulation of the globus pallidus or subthalamic nucleus meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage in the following patients:

- Those with Parkinson's disease with **ALL** of the following:
  - A good response to levodopa;

    AND
  - A minimal score of 30 points on the Unified Parkinson Disease Rating Scale when the patient has been without medication for approximately 12 hours;

    AND
  - Motor complications not controlled by pharmacologic therapy.

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

Contraindications to deep brain stimulation include:

- Patients who are not good surgical risks because of unstable medical problems or because of the presence of a cardiac pacemaker
- Patients who have medical conditions that require repeated magnetic resonance imaging (MRI)
- Patients who have dementia that may interfere with the ability to cooperate
- Patients who have had botulinum toxin injections within the last 6 months

Deep brain stimulation for other movement disorders, including but not limited to multiple sclerosis, post-traumatic dyskinesia, and tardive dyskinesia, **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational**.

Deep brain stimulation for the treatment of chronic cluster headaches does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational**.

Deep brain stimulation for the treatment of other psychiatric or neurologic disorders, including but not limited to Tourette syndrome, depression, obsessive compulsive disorder anorexia nervosa, alcohol addiction, chronic pain, and epilepsy, **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational.**

Effective for dates of service prior to November 13, 2014:
Unilateral deep brain stimulation of the thalamus meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage in patients with disabling, medically unresponsive tremor due to essential tremor or Parkinson's disease.

Disabling, medically unresponsive tremor is defined as all of the following:
- Tremor causing significant limitation in daily activities
- Inadequate control by maximal dosage of medication for at least three months before implant

Unilateral or bilateral deep brain stimulation of the globus pallidus or subthalamic nucleus meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage in the following patients:

- Those with Parkinson's disease with **ALL** of the following:
  - A good response to levodopa;

    AND
  - A minimal score of 30 points on the Unified Parkinson Disease Rating Scale when the patient has been without medication for approximately 12 hours;

    AND
  - Motor complications not controlled by pharmacologic therapy.

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

Contraindications to deep brain stimulation include:
- Patients who are not good surgical risks because of unstable medical problems or because of the presence of a cardiac pacemaker
- Patients who have medical conditions that require repeated magnetic resonance imaging (MRI)
- Patients who have dementia that may interfere with the ability to cooperate
- Patients who have had botulinum toxin injections within the last 6 months

Deep brain stimulation for other movement disorders, including but not limited to multiple sclerosis, post-traumatic dyskinesia, and tardive dyskinesia, **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational**.

Deep brain stimulation for the treatment of chronic cluster headaches does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational**.

Deep brain stimulation for the treatment of other psychiatric or neurologic disorders, including but not limited to Tourette syndrome, depression, obsessive compulsive disorder anorexia nervosa, alcohol addiction, chronic pain, and epilepsy, **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational.**

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

This policy was updated with a literature review of the MEDLINE database through February 05, 2018.

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 Deep Brain Stimulation of the Thalamus for Tremor

- 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 eight years, and side effects of stimulation were reported as mild and largely reversible.
- These results are at least as good as those associated with thalamotomy. An additional benefit of deep brain stimulation is that recurrence of tremor may be managed by changes in stimulation parameters.

Studies identified in subsequent literature searches supported the conclusions of the TEC Assessment. In 2008, Schuurman et al reported five-year follow-up of 65 patients comparing thalamic stimulation and thalamotomy for treatment of tremor due to Parkinson's disease (PD; 45 patients), essential tremor (ET; 13 patients), and multiple sclerosis (MS; 10 patients). After 5 years, 48 patients were available for follow-up: 32 with PD, 10 with ET, and 6 with MS. The primary outcome measure was functional status on the Frenchay Activities Index (FAI); secondary measures were tremor severity, frequency of complications, and patients' assessment of outcome. The mean difference in FAI scores was 4.4 (95% confidence interval [CI], 1.1 to 7.7) after 6 months, 3.3 (95% CI, -0.03 to 6.6) after 2 years, and 4.0 (95% CI, 0.3 to 7.7) after 5 years in favor of stimulation. Tremor suppression was equally effective after both procedures, and stable in PD patients. A diminished effect was observed 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 post-surgery, 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, and trunk). Three patients died of unrelated causes, one patient was lost to follow-up due to transfer of care, and one 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 ($p<0.01$). Bilateral stimulation at months three and 12 was significantly better than unilateral stimulation at month three ($p<0.05$). Small sample size limited analysis at months 24 and 36. Dysarthria was reported in six (27%) patients and disequilibrium in five patients after bilateral stimulation in staged implantations. No patient reported dysarthria and two reported disequilibrium before bilateral stimulation.

In 2006, Pahwa et al reported on long-term follow-up of 45 patients who underwent thalamic DBS of whom 26 had ET; 18 patients with ET had unilateral and eight had bilateral implantation. Sixteen patients with unilateral and seven with bilateral stimulators completed at least part of the five-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 five-year follow-up ($p=0.02$) and 36% improvement in activity of daily living (ADL) scores. Unilateral stimulation patients 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, such as dysarthria and other speech difficulties, disequilibrium or balance difficulties, and 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 Food and Drug Administration [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. A new technology in DBS systems, using directional leads, has recently emerged and data evaluating the new technology is expected to be published in 2018.

Symptoms Associated with Parkinson Disease

Advanced Parkinson Disease

Stimulation of the Globus Pallidus and Subthalamic Nucleus

This section was based on a 2001 TEC Assessment that focused on the use of DBS of the globus pallidus and subthalamic nucleus for a broader range of PD symptoms. The Assessment concluded:

- A wide variety of studies consistently demonstrate that deep brain stimulation of the globus pallidus or subthalamic nucleus 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 Parkinson's disease during periods when medication is not working, and in the case of

bilateral deep brain stimulation of the subthalamic nucleus, reduction in the required daily dosage of levodopa and/or its equivalents. The magnitude of these changes is both statistically significant and clinically meaningful.

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

A 2014 systematic review of RCTs by Perestelo-Perez et al evaluated 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 of the studies exclusively involved bilateral STN and, in the 6th trial, half of the patients received stimulation to the STN and the other half had GPi stimulation. Motor function assessment was blinded in 2 studies and randomization method was described in 4 studies. Five studies reported motor function, measured by the Unified Parkinson's Disease Rating Scale–III (UPDRS). In the off-medication phase, motor function was significantly higher with DBS versus 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 versus control (WMD=4.36; 95% CI, 2.80 to 5.92; SMD=0.53). Meta-analyses of other outcomes (e.g., activities of daily living, quality of life, dementia, depression), also favored the DBS group.

An earlier (2006) systematic review included both RCTs and observational studies; this review 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 ADL by 50% over baseline, as measured by the UPDRS-II (decrease of 13.35 points of 52). There was a 28-point decrease in the UPDRS-III score (of 108), indicating a 52% improvement in the severity of motor symptoms while the patient was not taking medication. A strong relationship was found between the preoperative dose response to Levodopa and improvements in both the UPDRS II and III. The analysis found a 56% reduction in medication use, a 69% reduction in dyskinesia, and a 35% improvement in quality of life with subthalamic stimulation.

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

<u>Parkinson Disease with Early Motor Complications</u>

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 years, 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 who 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.

Globus Pallidus versus Subthalamic Nucleus 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 (e.g., 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 (e.g., 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 FDA approval through the Humanitarian Device Exemption (HDE) process. The HDE approval process is available for conditions that affect less than 4,000 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 deep brain stimulation in 201 patients represented in 34 manuscripts. There were three studies that reported at least 10 cases of primary dystonia. In these studies, clinical improvement ranged from 50% to 88%. A total of 21 pediatric patients were studied; 81% were older than seven years. Among these patients there was about 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 neuro destructive 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.

An industry-sponsored patient- and observer-blinded RCT pallidal neurostimulation in patients with refractory cervical dystonia was published by Volkmann et al in 2014. The study included 62 adult patients with cervical dystonia of at least 3 years of 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 randomly assigned to DBS (n=32) or sham stimulation (n=30). The primary outcome was change in the TWSTRS severity at 3 months at the end of the blinded study period; thereafter, all patients received open-label active stimulation. After 3 months, mean TWSTRS improved

by 5.1 points (95% CI, 3.5 to 7.0) in the neurostimulation group and by 1.3 (95% CI, 0.4 to 2.2) in the sham group. The between-group difference was 3.8 points (95% CI, 1.76 to 5.84; p=0.024). Findings were mixed on the pre-specified secondary outcomes. There was significantly greater improvement in the neurostimulation than in the sham group on the TWSTRS disability subscore and the Bain Tremor Scale, but not on the TWSTRS pain score or the Craniocervical Dystonia Questionnaire–24. 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. Eleven (31%) of the 35 adverse events were rated as serious. Additionally, 40 adverse events, 5 of which were considered serious, occurred during 9 months of the open-label extension period. During the study, 7 patients experienced dysarthria, slightly slurred speech which was not reversible in 6 of the 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 globus pallidus was examined as a treatment of tardive dyskinesia in a 2007 multicenter case series, with a double-blind evaluation at six months (comparison of symptoms in 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, quality of life, and mood in a series nine patients treated with DBS of the globus pallidus internus for tardive dystonia were reported by Gruber et al in 2009. One week and three to six months after surgery, Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) motor scores were improved by 56.4 +/- 26.7% and 74.1 +/- 15.8%, 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 to 90 months), BFMDRS motor scores were reduced compared to presurgical assessment by 83 +/- 12.2%, 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.

Epilepsy
Systematic Review
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 Clinical 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).

Long-term outcomes of the SANTE trial were reported by Salanova et al in 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 study, 39 (35%) of 110 patients had a device-related serious adverse event, Most of which occurred in the first several months after implantation. The most frequently reported serious adverse events were implant site infection (10% of patients) and lead(s) not within target (8.2% of patients). Seven deaths occurred during the study and none were considered to be device-related. Depression was reported in 41 (37%) patients over the study; in 3 cases, this was considered device-related. Memory impairment (non-serious) was reported in 30 (27%) patients during the study, half of which had a history of the condition. Although some patients appear to have benefited from treatment during the extended follow-up phase, the difference between groups in the blinded portion of the study, while significant, was overall modest.

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 non-treating 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 5-year follow-up of 68 patients in a study comparing 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 is insufficient evidence for drawing conclusions on the impact of DBS on health outcomes for this population.

Tourette Syndrome

Several systematic reviews of the literature on DBS for Tourette syndrome have been published, including 4 identified in the 2016 literature search. Most recent systematic reviews (i.e., those published in 2015 or 2016) qualitatively described the literature. Only Baldermann et al (2015) conducted pooled analyses of study data. The Baldermann review identified 57 studies on DBS for Tourette syndrome, 4 of which were randomized crossover studies. The studies included a total of 156 cases. Twenty-four studies included a single patient each and 4 had sample sizes of 10 or more (maximum, 18). Half of the patients (n=78) were stimulated in the thalamus and the next most common areas of stimulation were the global pallidus internus anteromedial part (n=44) and postventrolateral part (n=20). Two of the RCTs used thalamic stimulation, 1 used bilateral globus pallidus stimulation, and 1 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 the YGTSS, 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 the YGTSS and 54% and more than a 50% improvement. In addition, data were pooled from the 4 crossover RCTs; there were a total of 27 patients receiving DBS and 27 receiving 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). The authors noted that the effect size of 0.96 is considered to be a large effect.

Another systematic review from 2012 examined patient and target selection for DBS of Tourette syndrome. Most clinical trials for DBS in Tourette syndrome have targeted the medial thalamus at the crosspoint of the centromedian nucleus, substantia periventricularis, and nucleus ventro-oralis internus. Other targets that have been investigated include the subthalamic nucleus, caudate nucleus, globus pallidus internus, and the anterior limb of the internal capsule and nucleus accumbens. The review found no clear consensus in the literature for which patients should be treated and what the best target is. Additional study is needed to clarify these issues.

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. They received surgery for bilateral globus pallidus internus DBS and were randomized to the off-position first or the on-position first for 3 months followed by the opposite position for the next 3 months. Fifteen patients underwent surgery 14 were randomized and 13 completed assessments after both on- and off-phases. For the 13 study completers, the mean YGTSS scores were 80.7 (SD=12.0) in the off-stimulation phase and 68.3 (SD=18.6) in the on-stimulation phase. Mean difference n YGTSS scores was 12.4 (95% CI, 0.1 to 24.7) which was statistically significant (p=0.048) after Bonferroni correction. There was no between-group difference in YGTSS scores in patients who were randomized to the on-phase first or second. Three serious adverse events were reported, 2 related to surgery and 1 related to stimulation. The authors noted that the most effective target for DBS in Tourette syndrome patients' needs additional study.

Section Summary: Tourette Syndrome

A number of uncontrolled studies and 4 crossover RCTs have been published; in addition, there are several systematic reviews of the published literature. Most studies, including the RCTs, had small sample sizes (i.e., ≤15 patients) and they used a variety of DBS targets. A 2015 meta-analysis has suggested that DBS may 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 Headaches 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 results from a prospective crossover, double-blind, multicenter study in 11 patients with DBS of the posterior hypothalamus for severe refractory chronic cluster headache. The randomized phase compared active and sham stimulation during one-month periods, and was followed by a one-year open phase. Severity of cluster headache was assessed by the weekly attacks frequency (primary outcome), pain intensity, sumatriptan injections, emotional impact, and quality of life (SF12). During the randomized phase, no significant change in primary and secondary outcome measures was observed between active and sham stimulation. At the end of the open phase, six of 11 patients reported a decrease >50% in the weekly frequency of attacks.

Another research group from Europe has published several case series (potentially overlapping) on DBS of 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 effects in 16 patients with chronic cluster headaches and in one patient with neuralgiform headache; treatment failed in three of three patients who had atypical facial pain. Controlled studies are needed to evaluate the long-term safety and effectiveness of DBS for chronic cluster headaches.

Section Summary: Cluster Headache and Facial Pain

Several case series and a crossover RCT have been published on 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 DBS of treatment-resistant depression. A systematic review from 2014 identified 22 published reports with six different approaches/targets including the nucleus accumbens, ventral striatum/ventral capsule, subgenual cingulate cortex, lateral habenula, inferior thalamic nucleus, and medial forebrain bundle. Only 3 of the studies identified were controlled with sham stimulation periods, and as of December 2013, there were two unpublished multicenter RCTs evaluating subgenual cingulate cortex and ventral striatum/ventral capsule DBS that had been terminated due to futility (interim analysis demonstrating very low probability of success if trial was completed as planned). A 2015 systematic review identified a single published RCT on DBS for depression; this trial is described next.

Randomized Controlled Trials

An industry-sponsored ,double-blind RCT evaluating DBS of the ventral capsule/ventral striatum in patients with chronic treatment resistant depression was published by Dougherty et al (2015). The study 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) versus sham (n=14) DBS, followed by an open-label continuation phase. One patient, who was assigned to active treatment, dropped out of the study during the blinded treatment phase. The primary outcome was clinical response at 16 weeks, defined as 50% or greater improvement from baseline on the Montgomery-Asberg Depression Rating Scale (MADRS). A response was identified in 3 (20%) of 15 patients in the active treatment group and 2 (14%) of 14 patients in the sham control group. The between-group difference in response was not statistically significant (p=0.53). During the blinded treatment phase, psychiatric adverse events occurring more frequently in the active treatment group included worsening depression, insomnia, irritability, suicide ideation, hypomania, and mania. Psychiatric adverse events occurring more frequently in the sham control group were early morning awakening and purging. Findings of this study do not support the 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 higher at the end of the active stimulation phase (mean HAM-D score, 16.5) than 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 in initial nonresponders (23.0). Among initial responders, 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; findings may 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 than in the control group. More recently, 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 may not be generalizable.

Obsessive-Compulsive Disorder

Several systematic reviews evaluating DBS for OCD have been published. Two of these reviews included meta-analyses pooling study findings. Kisely et al (2014) included only double-blind RCTs of active versus 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 subthalamic nucleus (1 study).

Duration of treatment ranged from 2 to 12 weeks. All studies reported scores on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). This is a 10-item scale in which higher scores reflect more intense symptoms and a score of 24 or more (of a possible 40) is considered severe illness. Most studies designate a therapeutic response as a Y-BOCS reduction of 35% or more from the pretreatment baseline, with a reduction of 25-35% or more considered a partial response. Only 1 of the 5 studies reported proportion of responders 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. When data from the 5 studies were pooled, there was a statistically significantly greater reduction in the mean Y-BOCS in the active versus sham group (mean difference, -8.49; 95% CI, 12.18 to -4.80). The outcome measure, however, does not allow conclusions on whether the difference between groups is clinically meaningful. Trial authors reported 16 serious adverse events including 1 cerebral hemorrhage and 2 infections requiring electrode removal. Additionally, non-serious transient adverse events were reported including 13 reports of hypomania, 5 of increase in depressive or anxious symptoms and 6 of headaches.

A 2015 systematic review and meta-analysis by Alonso et al included studies of any type (including case reports) evaluating DBS for OCD and reporting changes on the Y-BOCS. The authors identified 31 studies (total N=116 patients). They did not report study type (i.e., controlled vs uncontrolled); however, the meta-analysis was only of 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 including the anterior limb of the interior capsule, the ventral capsule and ventral striatum, the nucleus accumbens or the ventral caudate nucleus. Of the remaining studies, 5 (27 patients) addressed subthalmic nucleus stimulation and 2 (6 patients) addressed stimulation of the inferior thalamic peduncle. Data were available from 14 studies (105 patients) on percentage of responders (i.e., >35% reduction in posttreatment Y-BOCS scores). Twelve studies provided patient-level data. A 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), disinhibition (23 patients), throbbing or flushing (12 patients) and feeling the extension leads (10 patients). The study reported benefits and risks of DBS stimulation but conclusions cannot be drawn about stimulation to any particular region or about the safety or efficacy of DBS for OCD compared with sham stimulation or an alternative 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 the Y-BOCS. Uncontrolled data suggest improvement in OCD symptoms after DBS treatment, but also 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 deep brain stimulation for anorexia nervosa, alcohol addiction, Alzheimer disease, Huntington disease and chronic pain consists of review articles or small case series. These are not adequate to make a determination of efficacy.

Summary of Evidence

For individuals who have essential tremor or tremor in Parkinson disease who receive deep brain stimulation (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 resulted in clinically significant tremor suppression and that outcomes after DBS were at last as good as thalamotomy. Subsequent studies reporting long-term follow-up supported the conclusions of the Assessment and found that tremors were effectively controlled 5-6 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 (e.g., speech, motor fluctuations) associated with Parkinson disease (advanced or >4 years in duration with early motor symptoms) who receive DBS of the globus pallidus interna (GPi) or subthalamic nucleus (STN), the evidence includes randomized controlled trials (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 of DBS of the GPi or STN have consistently demonstrated clinically significant improvements in outcomes (e.g., 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 Parkinson disease 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 and STN have reported mixed findings and have not shown that 1 type of stimulation was 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, case series, and an RCT. 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, 1 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 (≤10 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 the net health outcome. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have multiple sclerosis (MS) who receive DBS, the evidence includes 1 RCT. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. One RCT with 10 MS patients is insufficient evidence on which to draw conclusions about the impact of DBS on health outcomes 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 for DBS is unknown and 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; and 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 may 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 1 has reported the outcome of greatest clinical interest (therapeutic response rate), and that trial did not find a statistically significant benefit for DBS compared to sham treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 impact of DBS on health outcomes for these conditions. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

European Academy of Neurology

In 2016, the European Academy of Neurology published guidelines on neuromodulation in management of chronic pain. Due to “very low” quality of evidence, the Academy could not recommend deep brain stimulation (DBS) for treatment of neuropathic pain.

American Academy of Neurology

Essential Tremor

The American Academy of Neurology published an updated guideline on the treatment of essential tremor in 2011. There were no changes from the conclusions and recommendations of

the 2005 practice parameters regarding DBS for essential tremor. The guidelines stated that DBS of the thalamic nucleus may be used to treat medically refractory limb tremor (level C, possibly effective) but that there is insufficient evidence to make recommendations regarding the use of thalamic DBS for head or voice tremor (level U, treatment is unproven).

Parkinson Disease
The 2006 Guidelines from AAN on the treatment of PD with motor fluctuations and dyskinesia found that although the criteria are evolving, patients with PD who are considered candidates for DBS include levodopa-responsive, nondemented, and neuropsychiatrically intact patients who have intractable motor fluctuations, dyskinesia, or tremor. AAN concluded that DBS of the subthalamic nucleus may be considered as a treatment option in PD patients to improve motor function and to reduce motor fluctuations, dyskinesia, and medication usage (Level C – possibly effective), but found insufficient evidence to make any recommendations about the effectiveness of DBS of the globus pallidus or the ventral intermediate nucleus of the thalamus in reducing motor complications or medication usage, or in improving motor function in PD patients.

The 2010 Guidelines from AAN on the treatment of nonmotor symptoms of PD found insufficient evidence for the treatment of urinary incontinence with DBS of the subthalamic nucleus. AAN found that DBS of the subthalamic nucleus possibly improves sleep quality in patients with advanced PD. However, none of the studies performed DBS to treat insomnia as a primary symptom, and DBS of the subthalamic nucleus is not currently used to treat sleep disorders.

Tardive Syndromes
The 2013 guidelines from AAN on the treatment of tardive syndromes were updated in 2018. The latest guidelines state that "pallidal DBS possibly improves tardive dyskinesia and might be considered as a treatment for intractable tardive dyskinesia (Level C, which indicates that the treatment is possibly effective, based on ≥1 class II study and consistent with ≥2 class III studies).

European Society for the Study of Tourette Syndrome
The European Society for the Study of Tourette Syndrome published guidelines on DBS in 2011. The guidelines stated that DBS for Tourette syndrome is still in its infancy and that there were no randomized controlled trials that have included a sufficiently large number of patients. The Society suggested that DBS only be used in adult, treatment-resistant, and severely affected patients, and highly recommended that DBS be performed in the context of controlled and double-blind trials including larger and carefully characterized groups of patients.

Canadian Network for Mood and Anxiety Treatments
The Canadian Network for Mood and Anxiety Treatments' 2009 clinical guidelines for management of major depressive disorder in adults found emerging evidence to support DBS as an experimental intervention for patients with treatment-refractory depression. There was no consensus on the most effective target brain region for implantation, although 3 regions have been explored (subcallosal cingulated gyrus, nucleus accumbens, ventral caudate/ventral striatum region).

American Society for Stereotactic and Functional Neurosurgery et al
The American Society for Stereotactic and Functional Neurosurgery and the Congress of Neurosurgeons published a systematic review and guideline on DBS for OCD in 2014. The document concluded that there is a single level I study supporting the use of bilateral subthalamic nucleus DBS for medically refractory OCD and a single level II study supporting bilateral nucleus accumbens DBS for medically refractory OCD. It also concluded that the evidence on unilateral DBS is insufficient.

European Society for the Study of Tourette Syndrome
The European Society for the Study of Tourette Syndrome published guidelines on DBS in 2011. The guidelines state that DBS for Tourette syndrome is still in its infancy, and that there are no randomized controlled studies available including a sufficiently large number of patients. There was general agreement among the workgroup members that DBS should only be used in adult, treatment- resistant, and severely affected patients, and it was highly recommended that DBS be performed in the context of controlled and double-blind trials including larger and carefully characterized groups of patients.

National Institute for Clinical Excellence
The U.K.'s National Institute for Health and Care Excellence (NICE; previously the National Institute for Clinical Excellence) has published Interventional Procedure Guidance documents on DBS.

Tremor and Dystonia
In 2006, NICE made the same statement for use of DBS for treatment of tremor and dystonia. Unilateral and bilateral stimulation of structures responsible for modifying movements, such as the thalamus, the globus pallidus and the subthalamic nucleus, which interact functionally with the substantia Negra, are included in both guidance statements. The guidance stated: "Current evidence on the safety and efficacy of deep brain stimulation for tremor and dystonia (excluding Parkinson's disease) appears adequate to support the use of this procedure."

Refractory Chronic Pain Syndromes (excluding headache)
The 2011 guidance states that there is evidence that DBS is efficacious in some patients who are refractory to other forms of pain control and that this procedure may be used provided that normal arrangements are in place for clinical governance, consent, and audit. Patients should be informed that DBS may not control their chronic pain symptoms and that possible risks associated with this procedure include the small risk of death.

Intractable Trigeminal Autonomic Cephalgias
The 2011 guidance states that current evidence on the efficacy of DBS for intractable trigeminal autonomic cephalalgias (e.g., cluster headaches) is limited and inconsistent, and the evidence on safety shows that there are serious but well-known side effects.

Refractory Epilepsy
The 2012 guidance states that the evidence on the efficacy of DBS for refractory epilepsy is limited in both quantity and quality. The evidence on safety shows that there are serious but well-known side effects.

Parkinson Disease
In 2003, NICE stated that current evidence on the safety and efficacy of DBS for treatment of PD appears adequate to support the use of the procedure. The guidance noted that DBS should only be offered when Parkinson disease is refractory to best medical treatment.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Key Words:
Activa Tremor Control System, deep brain stimulation, dystonia, essential tremor, Parkinson's disease, Reclaim™ DBS therapy, obsessive compulsive disorder (OCD), Vercise ™, chronic cluster headaches

Approved by Governing Bodies:
In 1997, the Activa® Tremor Control System (Medtronic) was cleared for marketing by the U.S. Food and Drug Administration (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.

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.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP contracts: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT Codes:

Implantation of Electrodes

61850	Twist drill or burr hole for implantation of neurostimulator electrodes, cortical
***61863**	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; first array
***61864**	; as above, but with each additional array
***61867**	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; first array
***61868**	; as above, but with each additional array.

*The above 4 codes recognize the option of the implantation of electrodes using microelectrode recording or not. In addition, if the patient is undergoing bilateral implantation of electrodes, one of the "each additional array" codes may be used. In some instances, patients undergo bilateral implantation in a staged procedure.

Implantation of Pulse Generator

61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array; **OR**
61886	; as above, but with connection to two or more electrode arrays

Electronic Analysis

95970	Electronic analysis of implanted neurostimulator pulse generator system (e.g. rate, pulse amplitude, pulse duration, configuration of wave form, battery status, electrode selectability, output modulation, cycling, impedance and patient compliance measurements); simple or complex brain, spinal cord, or peripheral (i.e. cranial nerve, peripheral nerve, sacral nerve, neuromuscular) neurostimulator pulse generator/transmitter, without programming
95978	Electronic analysis of implanted neurostimulator pulse generator system (e.g., rate, pulse amplitude and duration, battery status, electrode selectability and polarity, impedance, and patient compliance measurements), complex deep brain neurostimulator pulse generator/transmitter, with initial or subsequent programming; first hour
95979	; each additional 30 minutes after first hour

Neurostimulator analysis and programming is classified as either simple (95970) or complex (95978-79). CPT codes 95978 and 95979 are time based. Simple neurostimulators are defined as those affecting three or fewer neurostimulatory parameters (e.g., pulse amplitude, duration, and frequency, number of electrode contacts) while a complex device affects more than three parameters. In the setting of deep brain stimulation for tremor control, it is anticipated that the neuro-programming and analysis would be classified as simple. However, deep brain stimulation of the globus pallidus and subthalamic nucleus stimulation requires intraoperative monitoring of more than one clinical feature, (i.e., rigidity, dyskinesia, and tremor) and the neuro-programming would probably be classified as complex.

Over time, patients may undergo several sessions of electronic analysis and programming to find the optimal programming parameters. CPT codes 95970, 95978, and 95979, described here, may be used.

HCPCS:	**L8680**	Implantable neurostimulator electrode, each
	L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
	L8686	Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension
	L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
	L8688	Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension

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Policy History:

Medical Policy Group, January 2009 **(3)**
Medical Policy Administration Committee, February 2009
Available for comment February 6-March 23, 2009
Medical Policy Group, June 2011; Updated Description, Key Points, and References
Medical Policy Group, December 2011: 2012 Code Updates – verbiage update to 95970
Medical Policy Group, June 2012 **(3):** 2012 Updates – Key Points & References
Medical Policy Panel, June 2013
Medical Policy Group, June 2013 **(3):** 2013 Updates to Policy statement – anorexia nervosa, alcohol addiction, and chronic pain added to list of disorders (not an all-inclusive list) considered not to meet criteria for coverage), Key Points & References
Medical Policy Group, October 2013 **(3):** Removed ICD-9 Procedure codes; no change in policy statement.
Medical Policy Group, May 2014 **(5):** 2014 Coding Update: Deleted code L8680 effective July 1, 2014.
Medical Policy Group, June 2014 **(5):** Quarterly 2014 Coding Update: Code L8680 did not delete added back to policy under current codes.
Medical Policy Panel, November 2014
Medical Policy Group, November 2014 **(3):** Updates to Key Points, Key Words and References. Policy statement updated to include bilateral deep brain stimulation of thalamus as meeting criteria for disabling, medically unresponsive tremor in both limbs due to essential tremor or Parkinson disease.
Medical Policy Administration Committee, December 2014
Available for comment December 16 through January 29, 2015\
Medical Policy Panel, April 2016
Medical Policy Group, April 2016 **(6):** Updates to Key Points and References; clarification made to Policy statement – no change in policy intent.
Medical Policy Panel, April 2017
Medical Policy Group, May 2017 **(6)**: Updates to Key Points, Governing Bodies and References.
Medical Policy Panel, April 2018
Medical Policy Group, May 2018 **(6)**: Updates to Key Points, Governing Bodies and References.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.