# Deep Brain Stimulation (DBS)

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## DESCRIPTION

Deep brain stimulation (DBS) delivers electrical pulses to select areas of the brain (e.g., hypothalamus, thalamus, globus pallidus, subthalmic nucleus). DBS is used as an alternative to permanent neuroablative procedures for control of essential tremor (ET) and Parkinson's disease (PD). Deep brain stimulation (DBS) is also being evaluated for the treatment of variety of other neurological and psychiatric disorders, including but not limited to medically refractory epilepsy, dystonia, other movement disorders, cluster headache, Tourette syndrome, treatment resistant depression, and obsessive- compulsive disorder (OCD), drug addition, appetite disorders (anorexia nervosa and refractory obesity), impulsive or violent behavior and Alzheimer disease/dementias.

Deep brain stimulation (DBS) involves the stereotactic placement of electrodes into the brain (i.e., hypothalamus, thalamus, globus pallidus, or subthalamic nucleus). The mechanism of action is not completely understood, but the goal of DBS is to interrupt the pathways responsible for the abnormal movements associated with movement disorders such as Parkinson's disease (PD) and essential tremor (ET). The exact location of

electrodes depends on the type of disorder being treated, and unlike surgical ablation, which causes permanent destruction of the targeted area, DBS is reversible and adjustable. The DBS device consists of an implantable pulse generator (IPG) or neurostimulator, and implantable lead with electrodes and a connecting wire. Subcutaneous extension wires connect the lead(s) to the pulse generator (neurostimulator) which is implanted near the clavicle or, in the case of younger individuals with primary dystonia, in the abdomen.

Conventional deep brain stimulation systems deliver stimulation using cylindrical electrodes or Ring Mode (omnidirectional) stimulation which, stimulates neurons around the entire circumference of the lead, Directional deep brain stimulation uses a directional lead designed to steer electrical current to relevant areas of the brain while avoiding areas that may cause side effects.

A few weeks after the surgery, the pulse generator (neurostimulator) is activated in the doctor's office using a special remote control. The amount of stimulation is dependent on the condition being treated and may take as long as four to six months to find the optimal setting. The stimulation can be continuous, 24 hours a day, or the doctor may advise to turn the pulse generator off a night and back on in the morning, depending on the condition being treated. In some situations, the doctor may program the pulse generator to let the individual make minor adjustments at home using a special remote control. The battery life of a non-rechargeable stimulator is 3-5 years, depending upon how much stimulation the individual receives each day. Rechargeable neurostimulation last longer, about 9 years. When the battery needs to be replaced, the surgeon will replace the pulse generator during an outpatient procedure the leads implanted to the brain do not need to be replaced.

Deep brain stimulation (DBS) does not cure the disease, if deep brain stimulation (DBS) works, symptoms may improve significantly, but they usually do not go away completely. In some cases, medications may still be needed for certain conditions.

**Essential Tremor and Tremor in Parkinson's Disease**

**Clinical Context and Therapy Purpose**
Deep brain stimulation has been investigated as an alternative to permanent neuroablative procedures, such as thalamotomy and pallidotomy, and pharmacologic therapy.

Essential tremor (ET) is a common movement disorder afflicting millions of Americans. It is characterized primarily by an action and postural tremor most often affecting the arms, but it can also affect other body parts. Essential tremor (ET) is a progressive neurological disorder and can result in severe disability in some individuals. Although there is no cure for essential tremor, pharmacotherapy and surgery can provide some relief. Individuals with medication-resistant tremor may benefit from thalamotomy or deep brain stimulation (DBS) of the thalamus. Medical and surgical interventions can provide benefit in up to 80% of patients with essential tremor.

Deep brain stimulation (DBS) is also an effective treatment for individuals with advanced Parkinson's disease (PD) and motor complications that can no longer be improved by adjustment of medical therapy. The most common targets for implantation of deep brain stimulators (DBS) are the subthalamic nucleus and globus pallidus internus.

**Populations**
The relevant populations of interest are individuals with essential tremor (ET), or tremor associated with Parkinson's Disease (PD).

**Interventions**
The therapy being considered is deep brain stimulation (DBS), unilateral or bilateral stimulation of the thalamus as well as stimulation of the internal segment of the globus pallidus Internus and subthalmic nucleus.

**Comparators**
Essential tremor (ET) and Parkinson's disease (PD) are usually treated with medication. Surgery may be considered in people who respond poorly to medication, have severe side-effects, or have severe fluctuations in response to medication.

**Outcomes**
Outcomes include motor scores, mobility, disability, activities of daily living (ADLs) and quality of life (QOL).

Safety outcomes include death, stroke, depression, cognition, infection, and other device and procedure related event.

Length of follow-up was up to 5 years.

**Unilateral Stimulation of the Thalamus**
Blue Cross and Blue Shield Association (BCBSA) TEC assessment completed focused on unilateral deep brain stimulation (DBS) of the thalamus as a treatment of tremor. The assessment concluded:

- Tremor suppression was 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.

BCBSA TEC assessment found that unilateral DBS of the thalamus for patients with disabling, medically unresponsive tremor due to essential tremor or Parkinson's disease met the BCBSA Technology Evaluation Center (TEC) criteria. 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.

**Bilateral Stimulation of the Thalamus**

Putzke et. al. reported on series of 22 patients with essential tremor (ET) treated with bilateral -deep brain stimulation for management of midline tremor (head, voice, tongue, trunk). Patients were evaluated at baseline (pre-surgical) and postoperatively at 1, 3 and 12 months, and annually thereafter. The tremor rating scale was the primary outcome measure. Midline tremor showed significant improvement with stimulation "on" at nearly every postoperative interval when compared with stimulation "off" and with baseline tremor. Bilateral stimulation was associated with a significant incremental improvement in midline tremor control compared with unilateral stimulation: average "stimulation on" percentage change in midline tremor from the unilateral to bilateral period was 81%. Head and voice tremor showed the most consistent improvement. Among those requiring a change in stimulation parameters because of side effects, dysarthria, disequilibrium, motor disturbances, and paraesthesiae were the most common. Dysarthria was more common with bilateral (n = 6; 27%) than with unilateral (n = 0) stimulation. Stimulation parameters remained largely unchanged after the first three months. Nine of 44 leads placed (20%) required subsequent repositioning or replacement. The authors concluded thalamic stimulation is generally an effective approach for management of midline tremor associated with essential tremor. Although unilateral stimulation results in improvement, bilateral stimulation offers a significant further increment in midline tremor control. The results tend to be maintained over time and do not require a systematic increase in stimulation parameters. Adverse effects are generally mild and can be controlled by adjustment to the stimulation parameters.

Pahwa et. al. reported on the long- term safety and efficacy of deep brain stimulation (DBS) of the ventralis intermedius nucleus (VIM) of the thalamus for Parkinson’s disease (PD) and essential tremor (ET). Thirty-eight of 45 patients enrolled at five sites completed a 5-year follow-up study. There were 26 patients with ET and 19 with PD undergoing 29 unilateral (18 ET/11 PD) and 16 bilateral (eight ET/eight PD) procedures. Patients with ET were evaluated using the Tremor Rating Scale, and patients with PD were evaluated using the Unified Parkinson's Disease Rating Scale. The mean age of patients with ET was 70.2 years and 66.3 years in patients with PD. Unilaterally implanted patients with ET had a 75% improvement of the targeted hand tremor; those with bilateral implants had a 65% improvement in the left hand and 86% in the right compared with baseline. Parkinsonian patients with unilateral implants had an 85% improvement in the targeted hand tremor and those with bilateral implants had a 100% improvement in the left hand and 90% improvement in the right. Common DBS-related adverse events in patients receiving unilateral implants were paresthesia (45%) and pain (41%), and in patients receiving implants bilaterally dysarthria (75%) and balance difficulties (56%) occurred. Device-related surgical revisions other than IPG (implantable pulse generator) replacements occurred in 12 (27%) of the 45 patients. The authors concluded thalamic stimulation is safe and effective for the long-term management of essential and Parkinsonian tremors.

**Summary of Evidence**
For individuals who have essential tremor or tremor in Parkinson's disease who receive deep brain stimulation (DBS) of the thalamus, a TEC Assessment (systematic review) concluded there was sufficient evidence that deep brain stimulation (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.

**Symptoms Associated with Parkinson's Disease (PD)**

**Advanced Parkinson Disease (PD)**

**Stimulation of the Internal Segment of the Globus Pallidus Internus and Subthalmic Nucleus**
Blue Cross and Blue Shield Association (BCBSA) TEC assessment focused on the use of deep brain stimulation (DBS) of the internal segment of the globus pallidus internus (GPi) and subthalmic nucleus (STN) for a broader range of Parkinson's disease (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 medication is not working, and, in the case of bilateral DBS of the STN, reduction in the required 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 non-ablative and reversible.

BCBSA TEC assessment found that bilateral deep brain stimulation (DBS) of the subthalmic nucleus (STN) or the globus pallidus internus (GPi) for patients with advanced Parkinson's disease meets the BCBSA Technology Evaluation Center (TEC) criteria.

A systematic review of randomized controlled trials (RCTs) by Perestelo-Perez et. al. (2014) compared the impact of deep brain stimulation (DBS) plus medication versus

medication alone or plus sham DBS in Parkinson's disease (PD) outcomes. Outcome measures were motor function, waking time on good functioning without troublesome dyskinesias, levodopa-equivalent dose reduction, medication-induced complications, activities of daily living, health-related quality of life, and neurocognitive and psychiatric effects. Six RCTs (n = 1,184) that compared DBS plus medication versus medication alone were included. The results show that DBS significantly improves patients' symptoms, functionality, and quality of life. Effects sizes are intense for the reduction of motor signs and improvement of functionality in the off-medication phase, in addition to the reduction of the required medication dose and its associated complications. Moderate effects were observed in the case of motor signs and time in good functionality in the on-medication phase, in addition to the quality of life. Although the number of RCTs obtained is small, the total sample size is relatively large, confirming the efficacy of DBS in the control of motor signs and improvement of patients' functionality and quality of life. More controlled research is required on the neurocognitive and psychiatric effects of DBS.

An earlier systematic review by Kleiner-Fisman et. al. included both randomized controlled trials (RCTs) and observational studies; reviewers examined the literature on subthalamic nucleus (STN) stimulation for patients with Parkinson's disease (PD) who had failed medical management. Estimates of change in absolute Unified Parkinson's Disease Rating Scale (UPDRS) scores after surgery were generated using random-effects models. Sources of heterogeneity were explored with meta-regression models, and the possibility of publication bias was evaluated. Patient demographics, reduction in medication requirements, change in dyskinesia, daily offs, quality of life, and a ratio of postoperative improvement from stimulation compared to preoperative improvement by medication from each study were tabulated and average scores were calculated. Adverse effects from each study were summarized. Thirty-seven cohorts were included in the review. Twenty-two studies with estimates of standard errors were included in the meta-analysis. The estimated decreases in absolute UPDRS II (activities of daily living) and III (motor) scores after surgery in the stimulation ON/medication off state compared to preoperative medication off state were 13.35 (95% CI: 10.85-15.85; 50%) and 27.55 (95% CI: 24.23-30.87; 52%), respectively. Average reduction in L-dopa equivalents following surgery was 55.9% (95% CI: 50%-61.8%). Average reduction in dyskinesia following surgery was 69.1% (95% CI: 62.0%-76.2%). Average reduction in daily off periods was 68.2% (95% CI: 57.6%-78.9%). Average improvement in quality of life using PDQ-39 was 34.5% +/- 15.3%. Univariable regression showed improvements in UPDRS III scores were significantly greater in studies with higher baseline UPDRS III off scores, increasing disease duration prior to surgery, earlier year of publication, and higher baseline L-dopa responsiveness. Average baseline UPDRS III off scores were significantly lower (i.e., suggesting milder disease) in later than in earlier studies. In multivariable regression, L-dopa responsiveness, higher baseline motor scores, and disease duration were independent predictors of greater change in motor score. No evidence of publication bias in the available literature was found. The most common serious adverse event related to surgery was intracranial hemorrhage in 3.9% of patients. Psychiatric sequelae were common. Synthesis of the available literature indicates that

STN DBS improves motor activity and activities of daily living in advanced PD. Differences between available studies likely reflect differences in patient populations and follow-up periods. These data provide an estimate of the magnitude of the treatment effects and emphasize the need for controlled and randomized studies.

Tan et al. (2016) conducted a systematic review and meta-analysis to compare deep brain stimulation (DBS) of globus pallidus internus (GPi) and subthalamic nucleus (STN) which are the most targeted locations for the procedure. Clinical outcomes of motor function, non-motor function, and quality of life (QOL) were collected for the meta-analysis. Ten eligible trials with 1,034 patients were included in the analysis. Unified Parkinson's disease rating scale III (UPDRS-III) scores were collected at 6, 12, and 24 months post-surgery separately to assess the motor function of the patients. A statistically significant effect in favor of the GPi DBS was obtained in the off-medication/on-stimulation phase of UPDRS-III at 12 months. However, GPi DBS showed an opposite result at 24 months. In the on-medication/on-stimulation phase, GPi DBS obtained a worse outcome compared with STN DBS. Compared with STN DBS, increased dosage of levodopa equivalent doses was needed in GPi DBS. Meanwhile, Beck Depression Inventory II scores demonstrated that STN has a better performance. As for neurocognitive phase postsurgery, GPi DBS showed better performance in three of the nine tests, especially in verbal fluency. Use of GPi DBS was associated with a greater effect in eight of the nine subscales of QOL. The authors concluded that GPi and STN DBS significantly improve advanced Parkinson's patients' symptoms, functionality, and QOL. According to the authors, the question regarding which target is superior remains open for discussion. An understanding of the target selection depends on individual symptoms, neurocognitive/mood status, therapeutic goals of DBS (e.g., levodopa reduction), and surgical expertise.

**Parkinson’s Disease (PD) with Early Motor Complications**

Schuepbach et. al. (2013) published a randomized controlled trial (RCT) evaluating the deep brain stimulation (DBS) in patients with Parkinson’s disease (PD) and early motor complications. Key eligibility criteria included age 18 to 60 years; disease duration of 4 years of more; improvement of motor signs of 50% or more with dopaminergic medication; and a disease severity rating below stage 3 in the on-medication condition. A total of 251 patients were enrolled, 124 who were assigned to DBS plus medical therapy and 127 to medical therapy alone. Analysis was intention to treat and blind outcome assessment was done at baseline and at 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 of 39 points, with higher scores indicating higher QOL (quality of life). Mean baseline scores on the PDQ-39 were 30.2 in the DBS plus medical therapy group and 30.2 in the medical therapy only group. At 2 years, the mean score increased by 7.8 points in the DBS plus medical therapy group and decreased by 0.2 points in the medical therapy only group (mean change between groups, 8.0; $p=0.002$). There were also significant between-group differences in major secondary outcomes, favoring the DBS plus medical therapy group ($p<0.01$ on each): 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. This included 26 serious adverse events in the DBS group that were surgery- or device-related; reoperation was necessary in 4 patients. The authors concluded that neurostimulation was superior to medical therapy alone at a relatively early stage of Parkinson disease (PD) before the appearance of severe disabling motor complications. Neurostimulation may be a therapeutic option for patients at an earlier stage than current recommendations suggest.

**Globus Pallidus Internus (GPi) versus Subthalamic Nucleus (STN) Deep Brain Stimulation**

Several meta-analyses have compared the efficacy of globus pallidus internus (GPi) and subthalamic nucleus (STN) deep brain stimulation in Parkinson's disease (PD) patients.

The meta-analysis of randomized controlled trials (RCTs) by Tan et. al. (2016) compared the efficacy of globus pallidus internus (GPi) and subthalamic nucleus (STN) deep brain stimulation (DBS) for advanced Parkinson's disease (PD). Ten eligible trials with 1,034 patients were included in the analysis. Unified Parkinson disease rating scale III (UPDRS-III) scores were collected at 6, 12, and 24- months post-surgery separately to assess the motor function of the patients. A statistically significant effect in favor of the GPi DBS was obtained in the off-medication/on-stimulation phase of UPDRS-III at 12 months (mean difference [MD] =6.87, 95% confidence interval [95% CI]: 3.00–10.74, P=0.57, I2=0%). However, GPi DBS showed an opposite result at 24 months (MD =−2.46, 95% CI: −4.91 to −0.02, P=0.05, I2=0%). In the on-medication/on-stimulation phase, GPi DBS obtained a worse outcome compared with STN DBS (MD =−2.90, 95% CI: −5.71 to −0.09, P=0.05, I2=0%). Compared with STN DBS, increased dosage of levodopa equivalent doses was needed in GPi DBS (standardized MD =0.60, 95% CI: 0.46–0.74, P,0.00001, I2=24%). Meanwhile, Beck Depression Inventory II scores demonstrated that STN has a better performance (standardized MD =−0.31, 95% CI: −0.51 to −0.12, P=0.002, I2=0%). As for neurocognitive phase post-surgery, GPi DBS showed better performance in three of the nine tests, especially in verbal fluency. Use of GPi DBS was associated with a greater effect in eight of the nine subscales of QOL (quality of life). The authors concluded globus pallidus (GPi) stimulation and subthalamic nucleus (STN) stimulation significantly improve advanced Parkinson patients' symptoms, functionality, and QOL (quality of life). Variable therapeutic efficiencies were observed in both procedures, GPi and STN DBS. GPi DBS allowed greater recovery of verbal fluency and provided greater relieve of depression symptoms. Better QOL was obtained using GPi DBS. Meanwhile, GPi DBS was also associated with higher levodopa equivalent doses. The question regarding which target is superior remained open for discussion. An understanding of the target selection still depends on individual symptoms, neurocognitive/mood status, therapeutic goals of DBS (e.g. levodopa reduction) and surgical expertise.

In a meta-analysis, Peng et al. (2018) assessed the long-term efficacy of deep brain stimulation (DBS) of the subthalamic nucleus (STN) and globus pallidus interna (GPi) for Parkinson disease (PD). A total of 5 studies with 890 subjects (437 patients in the STN-DBS group and 453 patients in the GPi-DBS group) were included in the analysis. The study results showed no significant differences between STN-DBS and GPi-DBS in the long-term efficacy of unified Parkinson disease rating scale section (UPDRS) III scores including motor subtypes. The authors concluded that STN-DBS and GPi-DBS improve motor function and activities of daily living for PD.

**Directional Deep Brain Stimulation**

Two new deep brain stimulation (DBS) systems with directional leads are currently available, approved by the Food and Drug Administration (FDA) in 2016 and 2017. In 2016 the FDA approved the St. Jude Medical Infinity DBS device with directional lead technology designed to allow precise steering of the current towards the desired structural areas to optimize patient outcomes (reducing symptoms) and reduce side effects. In 2017 the FDA approved Vercise Deep Brain Stimulation System (Boston Scientific), this system is used as an adjunctive therapy from reducing motor symptoms of moderate to advanced levodopa responsive Parkinson's disease (PD) inadequately controlled with medication alone.

DBS device 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 deep brain stimulation (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.

In 2017, Dembek et. al. investigated whether deep brain stimulation (DBS) of the subthalamic nucleus in Parkinson's disease (PD) offers increased therapeutic windows, side-effect thresholds, and clinical benefit. In 10 patients, 20 monopolar reviews were conducted in a prospective, randomized, double-blind design to identify the best stimulation directions and compare them to conventional circular DBS regarding side-effect thresholds, motor improvement, and therapeutic window. In addition, circular and best-directional DBS were directly compared in a short-term crossover. Motor outcome was also assessed after an open-label follow-up of 3 to 6 months. Stimulation in the individual best direction resulted in significantly larger therapeutic windows, higher side-effect thresholds, and more improvement in hand rotation than circular DBS. Rigidity and finger tapping did not respond differentially to the stimulation conditions. There was no difference in motor efficacy or stimulation amplitudes between directional and circular DBS in the short-term crossover. Follow-up evaluations 3 to 6 months after implantation revealed improvements in motor outcome and medication reduction comparable to other DBS studies with a majority of patients remaining with a directional setting. The authors

concluded directional DBS can increase side effect thresholds while achieving clinical benefit comparable to conventional DBS.

**Summary of Evidence**
For individuals who have symptoms associated with Parkinson's disease (PD) (advanced or > 4 years in duration with early motor symptoms) who receive deep brain stimulation (DBS) of the globus pallidus interna (Gpi) or subthalamic nucleus (STN), the evidence includes randomized controlled trials (RCTs) and systematic reviews. 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 (e.g., neurologic function). Other systematic reviews have also found significantly better outcomes after DBS than after a control intervention. A randomized controlled trial (RCT) in individuals with levodopa-responsive Parkinson's disease of at least four years in duration and uncontrolled motor symptoms found that quality of life (QOL) at two 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 one type of stimulation is clearly superior to the other. The evidence is sufficient to determine that the technology results in meaningful improvement in the net health outcome.

**Neurologic and Psychiatric Disorders**

**Clinical Context and Therapy Purpose**
The role of deep brain stimulation (DBS) in treatment of other treatment resistant neurologic and psychiatric disorders, particularly medically refractory epilepsy, multiple sclerosis (MS), Tourette syndrome, major depressive disorders (treatment resistant depression), obsessive-compulsive disorder (OCD), appetite disorders (refractory obesity and anorexia nervosa), drug addiction, impulse or violent behavior, Huntington's disease, traumatic brain injury (TBI), chronic pain, and Alzheimer disease/dementias 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.

**Populations**
The population of interest are patients with other neurologic and psychiatric disorders.

**Interventions**
The therapy being considered is deep brain stimulation (DBS). Several target areas have been investigated.

**Comparators**
Alternative treatments vary by condition: standard of care.

**Outcomes**
The general outcomes of interest are symptoms, functional outcomes, quality of life, and treatment-related morbidity.

Safety outcomes include death, stroke, depression, cognition, infection and other device and procedure related events.

**Epilepsy**
It is estimated that approximately 30% of epileptic individuals do not respond to anti-epileptic drugs despite a reasonable trial of three or more antiepileptic medication (AEDs) and are considered to have drug-resistant epilepsy. Individuals with drug-resistant or medically refractory epilepsy have a higher risk of death as well as a high burden of epilepsy-related disabilities and limitations. Deep brain stimulation (DBS) has been proposed as a treatment for medically refractory epilepsy that persists in severity and/or frequency despite a reasonable trial of AEDs.

The relevant population(s) of interest are individuals with epilepsy refractory to medical treatment who are not candidates for respective surgery. The International League Against Epilepsy defined drug-resistant epilepsy as failure of adequate trials of two tolerated and appropriately chosen and used anti-epileptic drugs (AEDs), used either as monotherapy or in combination, to achieve seizure freedom.

The therapy being considered is deep brain stimulation (DBS). Several areas of the brain have been targeted.

The treatment of chronic epilepsy consists of anti-epileptic drugs. For individuals with epilepsy that are refractory to medical treatment, surgery options such as resection or disconnection may be considered.

*Vagus nerve stimulation may also be used in individuals with drug-refractory epilepsy who are not candidates for resective surgery, see also medical policy 07.01.60 Vagus Nerve Stimulation (VNS) and Vagal Blocking Therapy. Responsive neurostimulation (RNS) (cortical stimulation) may also be used in individuals for the treatment of refractory focal epilepsy, see medical policy 07.01.71 Responsive Neurostimulation for the Treatment or Refractory Focal Epilepsy.*

Outcomes include measure of seizure frequency or severity, response (reduction in seizure frequency by 50% or more), freedom from seizure, functional ability and disability, medication use, hospitalizations, and quality of life (QOL). The Quality-of-Life Inventory in Epilepsy (QOLIE-31) is a tool used to assess the impact of anti-epileptic treatment on individuals lives; the minimally important change in individuals with treatment-resistant seizures was 5 points.

**Systematic Reviews**

In 2017, Sprengers et. al. conducted a systematic review on deep brain and cortical stimulation for epilepsy. Despite optimal medical treatment, including epilepsy surgery, many epilepsy patients have uncontrolled seizures. Interest has grown in invasive intracranial neurostimulation as a treatment for these patients. Intracranial stimulation includes deep brain stimulation (DBS) (stimulation through depth electrodes) and cortical stimulation (subdural electrodes). The objective of the systematic review was to assess the efficacy, safety and tolerability of DBS and cortical stimulation for refractory epilepsy based on randomized controlled trials (RCTs). The selection criteria included RCTs comparing deep brain or cortical stimulation versus sham stimulation, resective surgery, further treatment with anti-epileptic drugs or other neurostimulation treatments (including vagus nerve stimulation). Twelve RCTs were identified, eleven of these compared one to three months of intracranial neurostimulation with sham stimulation. One trial was on anterior thalamic DBS (n = 109; 109 treatment periods); two trials on centromedian thalamic DBS (n = 20; 40 treatment periods), but only one of the trials (n = 7; 14 treatment periods) reported sufficient information for inclusion in the quantitative meta-analysis; three trials on cerebellar stimulation (n = 22; 39 treatment periods); three trials on hippocampal DBS (n = 15; 21 treatment periods); one trial on nucleus accumbens DBS (n = 4; 8 treatment periods); and one trial on responsive ictal onset zone stimulation (n =191; 191 treatment periods). In addition, one small RCT (n = 6) compared six months of hippocampal DBS versus sham stimulation. Evidence of selective reporting was present in four trials and the possibility of a carryover effect complicating interpretation of the results could not be excluded in five cross-over trials without any or a sufficient washout period. Moderate-quality evidence could not demonstrate statistically or clinically significant changes in the proportion of patients who were seizure-free or experienced a 50% or greater reduction in seizure frequency (primary outcome measures) after one to three months of anterior thalamic DBS in (multi)focal epilepsy, responsive ictal onset zone stimulation in (multi)focal epilepsy patients and hippocampal DBS in (medial) temporal lobe epilepsy. However, a statistically significant reduction in seizure frequency was found for anterior thalamic DBS (mean difference (MD), -17.4% compared to sham stimulation; 95% confidence interval (CI) -31.2 to -1.0; high quality evidence), responsive ictal onset zone stimulation (MD -24.9%; 95%CI -40.1 to -6.0; high-quality evidence) and hippocampal DBS (MD -28.1%; 95% CI -34.1 to -22.2; moderate-quality evidence). Both anterior thalamic DBS and responsive ictal onset zone stimulation do not have a clinically meaningful impact on quality life after three months of stimulation (high-quality evidence). Electrode implantation resulted in postoperative asymptomatic intracranial hemorrhage in 1.6% to 3.7% of the patients included in the two largest trials and 2.0% to 4.5% had postoperative soft tissue infections (9.4% to 12.7% after five years); no patient reported permanent symptomatic sequelae. Anterior thalamic DBS was associated with fewer epilepsy-associated injuries (7.4 versus 25.5%; P =0.01) but higher rates of self-reported depression (14.8 versus 1.8%; P = 0.02) and subjective memory impairment (13.8 versus 1.8%; P = 0.03); there were no significant differences in formal neuropsychological testing results between the groups. Responsive ictal onset

zone stimulation seemed to be well-tolerated with few side effects. The limited number of patients preclude firm statements on safety and tolerability of hippocampal DBS. With regards to centromedian thalamic DBS, nucleus accumbens DBS and cerebellar stimulation, no statistically significant effects could be demonstrated but evidence is of only low to very low quality. The authors concluded, except for one very small RCT, only short-term RCTs on intracranial neurostimulation for epilepsy are available. Compared to sham stimulation, one to three months of anterior thalamic DBS ((multi)focal epilepsy), responsive ictal onset zone stimulation ((multi)focal epilepsy) and hippocampal DBS (temporal lobe epilepsy) moderately reduce seizure frequency in refractory epilepsy patients. Anterior thalamic DBS is associated with higher rates of self-reported depression and subjective memory impairment. There is insufficient evidence to make firm conclusive statements on the efficacy and safety of hippocampal DBS, centromedian thalamic DBS, nucleus accumbens DBS and cerebellar stimulation. There is a need for more, large and well-designed RCTs to validate and optimize the efficacy and safety of invasive intracranial neurostimulation treatments.

In a meta-analysis and systematic review by Chang et. al. (2018) identified possible predictors of remarkable seizure reduction (RSR) for deep brain stimulation (DBS) in patients with refractory temporal lobe epilepsy (TLE). The authors conducted a comprehensive search of English-language literature published since 1990 that addressed seizure outcomes in patients who underwent DBS for refractory TLE. A pooled RSR rate was determined for eight included studies. RSR rates were analyzed relative to potential prognostic variables. The pooled RSR rate among 61 DBS-treated patients with TLE from 8 studies was 59%. Higher likelihood of RSR was found to be associated with lateralization of stimulation, lateralized ictal EEG findings, and a longer follow-up period. Seizure semiology, MRI abnormalities, and patient sex were not predictive of RSR rate. The best electrode type for RSR was the Medtronic 3389. Hippocampal and anterior thalamic nuclei (ATN) sites of stimulation had similar odds of producing RSR. The authors concluded that DBS is an effective therapeutic modality for intractable TLE, particularly in patients with lateralized EEG abnormalities and in patients treated on the ictal side. However, studies with higher levels of evidence and larger populations are needed to determine if DBS is effective for treating epilepsy.

Yan et. al. (2018) conducted a systematic review of deep brain stimulation (DBS) for the treatment of drug-resistant epilepsy (DRE) in childhood. Although deep brain stimulation has been studied in adults with DRE, little evidence is available to guide clinicians regarding the application of this potentially valuable tool in children. This systemic review aimed at understanding the safety and efficacy of DBS for DRE in pediatric populations, emphasizing patient selection, device placement and programming, and seizure outcomes. Inclusion criteria of individual studies were 1) diagnosis of DRE; 2) treatment with DBS; 3) inclusion of at least 1 pediatric patient (age ≤ 18 years); and 4) patient-specific data. Exclusion criteria for the systematic review included 1) missing data for age, DBS target, or seizure freedom; 2) nonhuman subjects; and 3) editorials, abstracts, review articles, and dissertations. This review identified 21 studies and 40 unique pediatric patients (ages 4–18 years) who received DBS treatment for epilepsy.

There were 18 patients with electrodes placed in the bilateral or unilateral centromedian nucleus of the thalamus (CM) electrodes, 8 patients with bilateral anterior thalamic nucleus (ATN) electrodes, 5 patients with bilateral and unilateral hippocampal electrodes, 3 patients with bilateral subthalamic nucleus (STN) and 1 patient with unilateral STN electrodes, 2 patients with bilateral posteromedial hypothalamus electrodes, 2 patients with unilateral mammillothalamic tract electrodes, and 1 patient with caudal zona incerta electrode placement. Overall, 5 of the 40 (12.5%) patients had an International League Against Epilepsy class I (i.e., seizure-free) outcome, and 34 of the 40 (85%) patients had seizure reduction with DBS stimulation. The authors concluded, prospective registries and future clinical trials are needed to identify the optimal DBS target, although favorable outcomes are reported with both CM and ATN in children.

Li et.al. (2018) reviewed the clinical evidence on the antiepileptic effects of deep brain stimulation (DBS) for drug resistant epilepsy, its safety, and the factors influencing individual outcomes. A comprehensive search of the medical literature (PubMed, Medline) was conducted to identify relevant articles investigating DBS therapy for drug-resistant epilepsy. Stimulation of the anterior nucleus of the thalamus (ANT) and hippocampus (HC) has been shown to decrease the frequency of refractory seizures. Half of all patients from clinical studies experienced a 46%-90% seizure reduction with ANT-DBS, and a 48%-95% seizure reduction with HC-DBS. The efficacy of stimulating other targets remains inconclusive due to lack of evidence. Approximately three-fourths of patients receiving ANT, HC, or centromedian nucleus of the thalamus (CMT) stimulation are responders-experiencing a seizure reduction of at least 50%. The time course of clinical benefit varies dramatically, with both an initial lesional effect and ongoing stimulation effect at play. Improved quality of life and changes to cognition or mood may also occur. Side effects are similar in nature to those reported from DBS therapy for movement disorders. Several factors are potentially associated with stimulation efficacy, including an absence of structural abnormality on imaging for ANT and HC stimulation, and electrode position relative to the target. Certain seizure types or syndromes may respond more favorably to specific targets, including ANT stimulation for deep temporal or limbic seizures, and CMT stimulation for generalized seizures and Lennox-Gastaut syndrome. The authors concluded we have identified several patient, disease, and stimulation factors that potentially predict seizure outcome following DBS. More large-scale clinical trials are needed to explore different stimulation parameters, reevaluate the indications for DBS, and identify robust predictors of patient response.

Bouwens ven der et. al (2019) conducted a systematic review of deep brain stimulation (DBS) for the anterior nucleus of the thalamus (ANT) for drug-resistant epilepsy. Despite the use of first-choice anti-epileptic drugs and satisfactory seizure outcome rates after resective epilepsy surgery, a considerable percentage of patients do not become seizure free. ANT-DBS may provide for an alternative treatment option in these patients. This literature review discusses the rationale, mechanism of action, clinical efficacy, safety, and tolerability of ANT-DBS in drug-resistant epilepsy patients. A review using systematic methods of the available literature was performed using relevant databases including Medline, Embase, and the Cochrane Library pertaining to the different aspects

ANT-DBS. ANT-DBS for drug-resistant epilepsy is a safe, effective and well-tolerated therapy, where a special emphasis must be given to monitoring and neuropsychological assessment of both depression and memory function. Three patterns of seizure control by ANT-DBS are recognized, of which a delayed stimulation effect may account for an improved long-term response rate. ANT-DBS remotely modulates neuronal network excitability through overriding pathological electrical activity, decrease neuronal cell loss, through immune response inhibition or modulation of neuronal energy metabolism. ANT-DBS is an efficacious treatment modality, even when curative procedures or lesser invasive neuromodulative techniques failed. When compared to vagus nerve stimulation (VNS), ANT-DBS shows slightly superior treatment response, which urges for direct comparative trials. Based on the available evidence ANT-DBS and VNS therapies are currently both superior compared to non-invasive neuromodulation techniques such as t-VNS and rTMS. Additional research is necessary in order to gain more insight into the mechanism of action of ANT-DBS in localization-related epilepsy which will allow for treatment optimization. Randomized clinical studies in search of the optimal target in well-defined epilepsy patient populations, will ultimately allow for optimal patient stratification when applying DBS for drug-resistant patients with epilepsy.

Hayes Technology Assessment published November 2019 and last reviewed January 2022 for deep brain stimulation (DBS) of the anterior nucleus of the thalamus for the treatment of refractory epilepsy after > antiepileptic drugs. The overall evidence is low, but it does suggest that DBS has the potential to reduce seizure frequency, severity and improve quality of life (QOL). This result has shown durability in long-term follow-up from a based on randomized controlled trial (RCT) as well as several observational studies. Continued studies are needed to determine the best DBS treatment parameters, and which patients would benefit most from this therapy.

**Randomized Controlled Trials (RCTs)**

Troster et. al. (2017) examined the incidence of memory and depression adverse events (AE) in the SANTE study during the 3- month blinded phase, and at 7- year follow-up during the open label noncomparative phase. No significant cognitive declines or worsening of depression scores were observed through the blinded phase or in open-label at 7-years. Higher scores were observed at 7 years on measures of executive functions and attention. Depression and memory-related AEs were not associated with reliable change on objective measures or 7-year neurobehavioral outcome. The AEs were without significant impact on life quality. Memory and depression AEs were not related to demographic or seizure characteristics, change in seizure frequency, frequency of AE or depression report.

Cukiert et. al. (2017) conducted a prospective, randomized, controlled, double-blind study to evaluate the efficacy of hippocampal deep brain stimulation (Hip-DBS) in patients with refractory temporary lobe epilepsy (TLE). Sixteen adult patients with refractory TLE were studied. Patients were randomized on a 1:1 proportion to an active (stimulation on) or to a control (no stimulation) arm. After implantation, patients were allowed to recover for 1 month, which was followed by a 1-month titration (or sham)

period. The 6-month blinded phase started immediately afterward. A postoperative MRI confirmed the electrode's position in all patients. All patients received bipolar continuous stimulation. Stimulus duration was 300 μs and frequency was 130 Hz; final intensity was 2 V. Patients were considered responders when they had at least 50% seizure frequency reduction. All patients had focal impaired awareness seizures (FIAS, complex partial seizures), and 87% had focal aware seizures (FAS, simple partial seizures). Mean preoperative seizure frequency was 12.5 ± 9.4 (mean ± standard deviation) per month. MRI findings were normal in two patients, disclosed bilateral mesial temporal sclerosis (MTS) in three, left MTS in five, and right MTS in six patients. An insertional effect could be noted in both control and active patients. In the active group (n = 8), four patients became seizure-free; seven of eight were considered responders and one was a non-responder. There was a significant difference regarding FIAS frequency between the two groups from the first month of full stimulation ($p < 0.001$) until the end of the blinded phase ($p < 0.001$). This was also true for FAS, except for the third month of the blinded phase. The authors concluded Hip-DBS was effective in significantly reducing seizure frequency in patients with refractory TLE in the active group, as compared to the control group. Fifty percent of the patients in the active group became seizure-free. The present study is the larger prospective, controlled, double-blind study to evaluate the effects of Hip-DBS published to date.

In 2019, Herman et. al. conducted a randomized double-blinded study using anterior thalamic deep brain stimulation (DBS) in refractory epilepsy. The safety and effect on seizure frequency of anterior thalamic nucleus deep brain stimulation were studied in this prospective, randomized, double-blinded study. Patients were followed for 12 months. The first 6 months were blinded with regard to active stimulation or not. After 6 months, all patients received active stimulation. Bilateral ANT electrodes were implanted into 18 patients suffering from focal, pharmacoresistant epilepsy. Antiepileptic treatment was kept unchanged from three months prior to operation. The Liverpool seizure severity scale (LSSS) was used to measure the burden of epilepsy. There was no significant difference between the 2 groups at the end of the blinded period at 6 months. However, when considering all patients and comparing 6 months of stimulation with baseline, there was a significant, 22% reduction in the frequency of all seizures ($P = 0.009$). Four patients had ≥50% reduction in total seizure frequency and 5 patients ≥50% reduction in focal seizures after 6 months of stimulation. No increased effect over time was shown. LSSS at 6 months compared to baseline showed no significant difference between the 2 groups, but a small, significant reduction in LSSS was found when all patients had received stimulation for 6 months. The authors concluded our study supports results from earlier studies concerning DBS as a safe treatment option, with effects even in patients with severe, refractory epilepsy. However, our results are not as encouraging as those reported from many other, mainly unblinded, and open studies.

**Observational Studies**

Kim et. al. (2017) conducted a retrospective chart review of 29 patients with refractory epilepsy treated with deep brain stimulation (DBS). The patients mean age was 31 years, had epilepsy for a mean of 19 years, and had a mean preoperative frequency of tonic-clonic seizures of 27 per month. The 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.

Jarvenpaa et. al. (2018) published a report of psychiatric adverse events in a series of 22 subjects treated with deep brain stimulation (DBS) of the anterior thalamus in patients with refractory epilepsy. Of the 22 subjects, 4 were reported to have had significant mood or psychiatric adverse events, 2 with prior history of depression and 2 without. The onset of adverse events varied considerably, occurring at 2 days through 5 years after active stimulation was initiated. The authors reported that in the 3 subjects with no prior history of mood or psychiatric conditions, altering DMS treatment parameters completely alleviated the symptoms. In the fourth subject, who had a prior history of depression and aggression, symptoms were decreased with parameter adjustments and medical management, but were not completely resolved. All 4 subjects experienced significant decreases in seizure activity throughout their treatment, with sustained benefit following adverse event-related adjustments. This study indicates that while mood and psychiatric adverse events are a concern with DBS treatment for epilepsy, with proper monitoring and management they can be alleviated or significantly reduced.

In 2019, Park et. al. reported on treatment outcomes of deep brain stimulation (DBS) of the anterior nucleus of the thalamus (ANT-DBS) in patients who had previously experienced vagus nerve stimulation (VNS) failure. Seven patients who had previously experienced VNS failure underwent ANT-DBS device implantation. VNS was turned off before DBS device implantation. Monthly seizure counts starting from baseline to 12-18 months after DBS were analyzed. Five (71.3%) of the 7 patients experienced a >50% reduction of seizure counts after DBS; 1 responder reached a seizure-free status after DBS therapy. Of the 2 non-responders, 1 subject showed improvement in seizure strength and duration, which lessened the impact of the seizures on the patient's quality of life. This is the first study in which favorable outcomes of ANT-DBS surgery were observed in individual patients with refractory epilepsy who had not responded to prior VNS. Further studies with a larger number of subjects and longer follow-up period are needed to confirm the feasibility of ANT-DBS in patients who have previously experienced VNS failure.

In 2021, Salanova et. al. reported the 10-year results of the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) randomized controlled trial. The results included the effectiveness and safety of deep brain anterior thalamus stimulation after seven and 10 years for the improvement in seizure reduction, and to report on the incidence of sudden unexpected death in epilepsy (SUDEP). A total of 73 subjects of the initial 110 (66%) were evaluated at the seven-year visit and 62/110 (56%) at the 10 year with an average age of 37.1 ± 11.8 years and 47.9% female. The average number of years with epilepsy was 22.5 ± 13.9 and the median baseline seizure per month was 17. Sixteen patients (21.9%) had previous resective surgery and 32 (43.8%) had a prior vagus nerve stimulation (VNS) implant. Primary outcomes measured included seizure severity (Liverpool Seizure Severity Scale) and quality of life in epilepsy (Quality of Life in

Epilepsy Inventory-31 [QOLIE-31] scale). Secondary outcomes included adverse event monitoring and the incidence of SUDEP. The sample of subjects used to determine the incidence of SUDEP included data from two sources: the SANTE study and the pilot studies at five centers. The median seizure frequency percent reduction from baseline at seven years was 75% ($p<0.001$) with 74% having ≥ 50% reduction in total seizures. Significant reductions were self-reported by subjects in the following areas: "most severe" seizures (71%), focal impaired awareness seizures (FIASs; 78%), focal to bilateral tonic–clonic seizures (FBTCSs; 71%), and focal aware seizures (FASs; 92%) ($p<0.010$ for all). Eighteen percent (n=20) were seizure free for six consecutive months, nine subjects (8%) for more than two years, one subject for five years and one for six years. At seven years, the median percent seizure reduction from baseline was 75% ($P<0.05$) for subjects who had previously tried VNS, 78% for those without prior VNS ($p<0.001$) and 69% ($p=0.084$) for those who had previous resective surgery. The subgroup analysis showed a median seizure reduction of 78% for temporal lobe seizures ($p<0.001$), 86% for frontal lobe seizures ($p=0.129$) and 39% ($p=0.320$) for other seizures at seven years of follow-up. The improvements from baseline on the Liverpool Seizure Severity Scale and QOLIE-31 reported in the five-year follow-up study were maintained at year seven (both measures, $p<0.001$) compared to baseline). Forty-three percent of subjects experienced a clinically meaningful change on the QOLIE-31, which is defined as a 5-point change from baseline. Eighty-four percent (54/64) of subjects reported that they were satisfied or greatly satisfied with the results of their therapy. There were no unanticipated serious adverse events. Events related to DBS or epilepsy from implant to 10 years, included implant site infection in 12.7% of subjects (1-year rate of 7.3%) and leads not within target in 8.2%. Most device related events occured during the operative phase. Other adverse events included depression in 37.3% of subjects (two thirds had history of depression), memory impairment in 30.0% of subjects (half had history of memory impairment), and suicidality in 10.0%. There were eight deaths in the study, one occurring prior to implant and not included in the calculations. No death was directly attributed by the investigator to the implant, device, or therapy. The SUDEP rate for the SANTÉ study was 2.1 deaths/1000 person-years, inclusive of definite or probable SUDEP. There was no SUDEP in the pilot follow-up subjects, bringing the overall rate to 2.0 deaths/1000 person-years, based on 1,014 person-years of device experience. The overall mortality rate in the study, based on seven subject deaths post implant, was 6.9 per 1000 person-years. Author noted limitations included the effect of discontinuation of subjects who did poorly and the use of adjunctive therapies, such as anti-seizure medications and their potential impact on the long-term results. The authors also noted that the study was not powered to address SUDEP rate variations. Long term results showed that with ongoing DBS therapy subjects continued a trend for improvement in seizure reduction.

**Summary of Evidence**

The evidence includes systematic reviews and meta-analysis, randomized controlled trials (RCTs) and observational studies in which deep brain stimulation (DBS) was evaluated for the treatment of medically refractory epilepsy. Results from the large scale Stimulation of the Anterior Nuclei of Thalamus for Epilepsy (SANTE) trial, a double-

blind RCT of DBS for epilepsy was reported by Fisher et.al., this study used a standard DBS device (Medtronic Mode 3387) stimulating the anterior nuclei. All subjects underwent DBS implantation followed by 3 months of randomized and blinded active stimulation (n=54) or no stimulation (n=55), then followed by 9 months of active stimulation for all subjects. A total of 110 subjects had DBS electrode implantation. Both the active and control groups demonstrated significant decreases in seizure activity through the blinded period. However, the control group trended towards baseline levels at the end of the third month. The active group had a sustained and significant decrease in seizure activity (p=0.0017). A statistically significant difference between groups was only seen in the third month, in favor of the stimulation group (p=0.0023). Subjects in the stimulation group experienced fewer seizure-related injuries (7.4%) versus the control group (25.5%, p=0.01). The authors state that DBS of the anterior nuclei in this population was mostly palliative in nature, but 14 participants (12.7%) became seizure-free for at least 6 months. Additionally, significant benefits were seen in some subjects who were not previously helped by multiple drugs, vagus nerve stimulation (VNS), or epilepsy surgery. Based on the SANTE trial data, the FDA granted pre-market approval on April 27, 2018 to the Medtronic Deep Brain Stimulation (DBS) Therapy System for the treatment of epilepsy with bilateral stimulation of the anterior nucleus of the thalamus (ANT) as an adjunctive therapy for reducing the frequency of seizures in individuals 18 years of age or older diagnosed with epilepsy characterized by partial-onset seizures, with or without secondary generalization, that are refractory to three or more antiepileptic medications.

While the available published peer-reviewed evidence addressing the use of DBS for medically refractory epilepsy is limited mostly to the SANTE trial results, use of this treatment approach has continued, and clinical experience has been gained. As a result, there is a growing body of expert experience and opinion addressing the complications specifically, the concerns regarding the incidence of sudden unexpected death in epilepsy (SUDEP) and depression. Expert opinion over the past decade has evolved to see SUDEP risk following DBS initiation as no greater than the SUDEP risk for individuals with medically refractory seizures. Similarly, the concerns about depression and mood disorders have been more clearly elucidated with the publication by Troster and colleagues. With that evidence it has been made clear that specific populations may suffer additional risk of depression or mood disturbances with DBS treatment. However, in the clinical setting there must be an assessment of balancing the risks due to insufficiently treated epilepsy versus the risks associated with depression and mood disturbances, and the predominant current consensus is that the risks posed by insufficiently treated epilepsy is greater. In summary, the population with medically refractory epilepsy for whom DBS has been proposed suffer from significant morbidity and mortality unrelieved by medical therapy. While some may be candidates for responsive neurostimulation (cortical stimulation) and resective surgical procedures, many are not. Some individuals may have also failed vagus nerve stimulation (VNS) for treatment of their medically refractory epilepsy. The use of this less invasive approach should be made available for these individuals with medically refractory epilepsy as an additional treatment option in accordance to the FDA approval indications for the Medtronic Deep Brain Stimulation

(DBS) Therapy System for the treatment of epilepsy with bilateral stimulation of the anterior nucleus of the thalamus (ANT) as an adjunctive therapy for reducing the frequency of seizures in individuals 18 years of age or older diagnosed with epilepsy characterized by partial-onset seizures, with or without secondary generalization, that are refractory to three or more antiepileptic medications.

**Multiple Sclerosis (MS)**
Multiple sclerosis (MS) is the most common immune-mediated inflammatory demyelinating disease of the central nervous system. MS is characterized pathologically by multifocal areas of the demyelination with loss of oligodendrocytes and astroglial scarring. Certain clinical features are typical of MS, but the disease has a highly variable pace and many atypical forms. Deep brain stimulation has been investigated for the treatment of MS tremor.

Schuurman et. al. 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 multiple sclerosis (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.

In 2020, Brandmeir et. al. examined the effect of deep brain stimulation (DBS) on multiple sclerosis (MS)-tremor, as measured by a normalized scale of tremor severity, with a meta-analysis of the published literature. Despite multiple studies completed on this topic at busy DBS centers, patient cohorts remain small. This is true even for case series and retrospective trials, indicating that MS tremor patients seeking DBS are relatively rare, especially compared to patients with essential tremor or Parkinson disease. Although this analysis shows that DBS improves tremor in MS, the exact magnitude to improvement that can be expected on a given tremor scale is difficult to predict. Going forward, it would improve the utility of studies on this topic to use an agreed upon, standardized measure of tremor severity. This would allow easier generalizability of results. Also, MS and lesions associated with tremor are varied. Other symptoms of MS (ataxia, anxiety) can also exacerbate tremor in ways independent of the pathway treated by DBS. Future studies will need to be done focused on selecting the patients with MS tremor who are most likely to benefit from surgery.

**Summary of Evidence**
Despite multiple studies completed on DBS for MS at busy DBS centers, patient cohorts remain small. One randomized controlled trial (RCT) reporting on 10 multiple sclerosis (MS) patients provides insufficient data for drawing conclusions on the efficacy of deep brain stimulation (DBS) for this population. Meta-analysis completed in 2020 by Brandmeir et. al. states future studies will need to be done focused on selecting the patients with MS tremor who are most likely to benefit from surgery. Further randomized controlled trials (RCTs) are needed with higher levels of evidence and larger populations to determine if DBS is effective in the treatment of MS. The evidence is insufficient to

determine that the technology results in a meaningful improvement in net health outcomes.

**Tardive Dyskinesia**
Tardive dyskinesia (TD) is a medication-induced hyperkinetic movement disorder associated with the use of dopamine receptor-blocking agents, including antipsychotic drugs and two antiemetic agents, metoclopramide and prochlorperazine. TD encompasses a wide range of abnormal, involuntary movements that often persist after discontinuation of the causative mediation. TD can be irreversible and lifelong. The condition can be disfiguring and disabling, with major negative impacts on psychologic health and quality of life (QOL). Deep brain stimulation (DBS) has been studied in the treatment of permanent disabling TD that is unresponsive to pharmacologic treatment modalities.

**Systematic Reviews**
In 2018 Macerolla et. al. completed a systematic review and meta-analysis on the available literature reporting on cases with either tardive dystonia or dyskinesia treated with deep brain stimulation (DBS). Among the broad entity of tardive syndromes, tardive dystonia and classical tardive dyskinesia sometimes require advanced treatments like deep brain stimulation of the globus pallidus internum (Gpi-DBS) or the subthalamic nucleus (STN-DBS). Thirty-four level VI studies and one level II study with 117 patients were included. Level I studies were not identified. Only four of the patients had tardive dyskinesia. All the others had tardive dystonia. The majority had Gpi-DBS (n = 109). Patients had a mean age of 47.4 years. The duration of follow-up was 25.6 months. The Abnormal Involuntary Movement Scale was reported in 51 patients with an improvement of 62 (15%) and the Burke-Fahn-Marsden scale was reported in 67 cases with an improvement of 76(21%). Reported adverse events were surgery-related in 7 patients, stimulation-induced in 12, and psychiatric in 3 patients. These reports thus suggest favorable effects of DBS and it seems to be relatively safe. DBS can be considered for patients with severe, medication-resistant symptoms. Controlled and randomized studies with blinded outcomes are needed.

**Randomized Controlled Trials**
Damier et. al. assessed the efficacy of bilateral deep brain stimulation of the internal part of the global pallidus to treat severe tardive dyskinesia (TD) in a prospective phase 2 multicenter study. Patients with severe TD refractory to medical treatment were studied to evaluate the severity of abnormal involuntary movements before and after 6 months of bilateral globus pallidus deep brain stimulation. A successful outcome was defined as a decrease of more than 40% in the main outcome measure at 6 months. The early stopping rule was invoked if the number of successful outcomes in 10 patients was fewer than 2, or 5 or more. A double-blind evaluation in the presence and absence of stimulation was performed at 6 months after surgery. Main Outcome Measure Change in score on the Extrapyramidal Symptoms Rating Scale. At 6 months after surgery, the Extrapyramidal Symptoms Rating Scale score had decreased compared with baseline by more than 40% (mean improvement, 61%; range, 44%-75%) in the first 10 patients included. In accord

with the 2-step open Fleming procedure, we ended the trial at the first step and concluded that pallidal stimulation is an effective treatment for TD. The efficacy of the treatment was confirmed by a double-blind evaluation, with a mean decrease of 50% (range, 30%-66%) (P = .002) in the Extrapyramidal Symptoms Rating Scale score when stimulation was applied compared with the absence of stimulation. There were no marked changes in the patients' psychiatric status. The authors concluded although these results need to be confirmed in a larger group of patients with a longer follow-up, bilateral globus pallidus deep brain stimulation seems to offer a much-needed new treatment option for disabling TD.

Gruber et. al. reported outcomes on motor function, quality of life (QOL) and mood in a series of 9 patients treated with deep brain stimulation (DBS) of the globus pallidus internus (GPi) in patients with tardive dystonia. Patients were assessed at 3 points: 1 week, 3 to 6 months and last follow-up at the mean of 41 (range of 18-80) months after surgery using established and validated movement disorder and neuropsychological scales. Clinical assessment was performed by a neurologist not blinded to the stimulation settings. One week and 3 to 6 months after globus pallidal DBS, Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) motor scores were ameliorated by 56.4 +/- 26.7% and 74.1 +/- 15.8%, BFMDRS disability scores by 62.5 +/- 21.0% and 88.9 +/- 10.3%, and Abnormal Involuntary Movement Scale (AIMS) scores by 52.3 +/- 24.1% and 69.5 +/- 27.6%, respectively. At last follow-up, this improvement compared with the pre-surgical assessment was maintained as reflected by a reduction of BFMDRS motor scores by 83.0 +/- 12.2%, BFMDRS disability scores by 67.7 +/- 28.0%, and AIMS scores by 78.7 +/- 19.9%. QOL (quality of life) improved significantly in physical components, and there was a significant improvement in affective state. Furthermore, cognitive functions remained unchanged compared with pre-surgical status in the long-term follow-up. No permanent adverse effects were observed.

**Case Series and Case Report**

Spindler et. al. (2013) completes a case report and review of the literature regarding globus pallidus deep brain stimulation (DBS) for tardive dyskinesia (TD). Tardive dyskinesia (TD) can be a disabling condition and is frequently refractory to medical therapy. Over the past decade there have been many reports of TD patients experiencing significant benefit with deep brain stimulation (DBS) of the globus pallidus interna (GPi). The growing literature on this treatment option for TD consists predominantly of case reports and series. The reported benefit ranges widely, but the majority of cases experienced at least a 50% improvement in symptoms. The anatomical distribution of dyskinesias has not clearly influenced outcome, though fixed postures appear less likely to improve than phasic movements. Onset of benefit can be immediate or take months, and benefit is sustained in most cases, for at least 6 months and up to several years. A wide variety of voltages, frequencies, and pulse widths have demonstrated efficacy. A small number of reports which examined psychiatric symptoms before and after surgery did not find any decline, and in some cases revealed improvement in mood. However, these overall positive results should be interpreted with caution, as the majority of reports lacked blinded assessments, control groups, or standardized therapy parameters.

Pouclet-Courtemanche et. al. (2016) reported on a case series of 19 patients with severe pharmaco-resistant tardive dyskinesia treated with deep brain stimulation (DBS). Patients were assessed after 3, 6 and 12 months after the procedure. At 6 months, all patients had a decrease of more than 40% on the ESRS (Extrapyramidal Symptoms Rating Scale). This improvement was maintained at 12 months ESRS score was 58% (range 21%-81%).

**Summary of Evidence**
For individuals who have tardive dyskinesia (TD) or tardive dystonia who receive deep brain stimulation (DBS) the evidence consists of case series, case report, randomized controlled trials and systematic reviews. Few studies were identified and had small sample sizes. While the literature may show some promise in individuals with refractory tardive dyskinesia (TD), additional studies are needed to include randomized controlled studies with longer follow-up and more individuals to establish the role of DBS for this indication. The evidence is insufficient to determine that the technology results in a meaningful improvement in net health outcomes.

**Treatment Resistant Depression**
Treatment resistant depression typically refers to major depressive episodes that do not respond satisfactorily after two trials of antidepressant monotherapy; however, the definition has not been standardized. Deep brain stimulation (DBS) has been investigated in the treatment of treatment resistant depression.

**Systematic Reviews**
A variety of target areas are being investigated for use of deep brain stimulation (DBS) for treatment-resistant depression. A systematic review by Morishita et. al. (2014) identified 22 clinical research papers with 5 unique DBS approaches using different targets, including nucleus accumbens, ventral striatum/ventral capsule (VC/VS), subgenual cingulate cortex (SCC), lateral habenula, inferior thalamic nucleus, and medial forebrain bundle. Among the 22 published studies, only 3 were controlled trials with sham stimulation periods, and 2 multicenter, randomized, controlled trials (RCTs) evaluating the efficacy of subgenual cingulate cortex and ventral striatum/ventral capsule DBS were discontinued owing to inefficacy based on futility analyses (interim analysis demonstrating very low probability of success if the trial was completed as planned). The authors concluded, in total, 6 different targets have been proposed and tried for major depressive disorder (MDD) DBS. Of these, only VC/VS and SCC DBS have been investigated with controlled trials with small sample sizes, and, unfortunately, recent multicenter, prospective, randomized trials have reportedly failed to confirm the efficacy of stimulation at these 2 targets (i.e., VC/VS and SCC). Despite these setbacks, the extraordinary public health burden of MDD and the promising results of various open-label trials warrant further investigation. No class I evidence exists in the literature supporting the efficacy of DBS for MDD, and the optimal DBS target for treatment-resistant depression remains unclear. DBS for MDD should therefore be considered experimental at present; further studies are indicated to clarify the malfunctioning neurocircuitry associated with MDD and to evaluate the efficacy and safety of the various

MDD DBS strategies. As always, surgical therapy for the treatment of psychiatric disorders should only be performed in the setting of a multidisciplinary team, which should include, as a minimum, a dedicated psychiatrist, neurologist, neurosurgeon, and neuropsychologist.

Berlim et al. (2014) conducted a systematic review and exploratory meta-analysis to investigate deep brain stimulation (DBS) applied to the subgenual cingulate cortex (SCC) as a potential treatment for severe and chronic treatment-resistant depression (TRD). Data from 4 observational studies were included in the analysis, totaling 66 subjects with severe and chronic TRD. Twelve-month response and remission rates following DBS treatment were 39.9% and 26.3%, respectively. Also, depression scores at 12 months post-DBS were significantly reduced. There was a significant decrease in depression scores between 3 and 6 months, but no significant changes from months 6 to 12. Finally, dropout rates at 12 months were 10.8%. The authors concluded that DBS applied to the SCC seems to be associated with relatively large response and remission rates in the short- and medium- to long-term in patients with severe TRD. Also, its maximal antidepressant effects are mostly observed within the first 6 months after device implantation. According to the authors, these findings are clearly preliminary and future controlled trials should include larger and more representative samples and focus on the identification of optimal neuroanatomical sites and stimulation parameters.

In a systematic review, Naesstrom et al. (2016) reviewed the current studies on psychiatric indications for deep brain stimulation (DBS), with focus on obsessive-compulsive disorder (OCD) and major depressive disorder (MDD). A total of 52 studies met the inclusion criteria with a total of 286 unique patients treated with DBS for psychiatric indications; 18 studies described 112 patients treated with DBS for OCD in six different anatomical targets, while nine studies included 100 patients with DBS for MDD in five different targets. The authors concluded that DBS may show promise for treatment-resistant OCD and MDD, but the results are limited by small sample size and insufficient randomized controlled data. According to the authors, other psychiatric indications are currently of a purely experimental nature.

Kisely et al. (2018) performed a systematic review and meta-analysis on the effectiveness of deep brain stimulation (DBS) in depression. Ten papers from nine studies met inclusion criteria, all but two of which were double-blinded randomized controlled trials (RCTs). The main outcome was a reduction in depressive symptoms. It was possible to combine data for 190 participants. Patients on active, as opposed to sham, treatment had a significantly higher response and reductions in mean depression score. However, the effect was attenuated on some of the subgroup and sensitivity analyses, and there were no differences for most other outcomes. In addition, 84 participants experienced a total of 131 serious adverse effects, although not all could be directly associated with the device or surgery. Finally, publication bias was possible. The authors concluded that DBS may show promise for treatment-resistant depression but remains an experimental treatment until further data are available.

A variety of target areas are being investigated for use of deep brain stimulation for treatment-resistant depression. Hitti et. al. (2020) conducted a meta-analysis and meta-regression of blinded studies that compared active deep brain stimulation to sham stimulation (12 trials, 186 patients). Anatomic targets included the ventral anterior limb of the internal capsule, ventral capsule/ventral striatum, subcallosal cingulate, inferior thalamic peduncle, medial forebrain bundle, and lateral habenula. The most common target was the subcallosal cingulate. Meta-analysis showed a modest reduction in depression rating scales (standardized MD, -0.75; 95% CI, -1.13 to -0.36; p<.001) with moderate heterogeneity across studies ($I^2$=59%). Meta-regression did not identify a significant difference between target areas. Adverse events included headache (26% of patients), visual disturbances (21%), worsening depression (16%), sleep disturbance (16%) and anxiety (14%).

In 2021. Wu et. al., conducted a meta-analysis of blinded studies that compared deep brain stimulation to control (placebo or sham stimulation). There were 17 studies included, with a total of 233 patients, however, the majority were open-label studies (n=15). Anatomic targets included subcallosal cingulate gyrus (n=8), ventral capsule/ventral striatum (n=2), epidural prefrontal cortical (n=2), nucleus accumbens (n=1), superior lateral branch of the medial forebrain bundle(n=2), posterior gyrus rectus (n=1) and ventral anterior limb of the interna capsule (n=1). The pooled response rate estimate for the 2 RCTs was 1.45 (95% CI, 0.50 to 4.21) and for the open-label studies it was 0.56 (95% CI, 0.43 to 0.69); there was significant heterogeneity ($I^2$ = 73.6%; p<.0001). The pooled estimate for remission rate in the open-label studies was 0.32 (95% CI, 0.25 to 0.39) with no statistical heterogeneity ($I^2$ = 30.3%; p=.127); the pooled estimate for adverse events in the open-label studies was 0.67 (95% CI, 0.54 to 0.80) with significant heterogeneity ($I^2$ =76.8%; p<.0001).

**Randomized Controlled Trials (RCTs)**

An industry-sponsored, double-blind RCT evaluating deep brain stimulation (DBS) targeting the ventral capsule/ventral striatum (VC/VS) 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 randomized controlled trial (RCT) evaluating active and sham phases of deep brain stimulation (DBS) 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 non-responders. 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 non-responders). 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.

In 2019, Crowell et. al. reported long-term follow-up of a within-subject trial with 28 participants with treatment-resistant depression or bi-polar II disorder who were treated with deep brain stimulation of the subcallosal cingulate.[59,] Patients were included who had depression for at least 12 months with non-response to at least 3 antidepressant medications, a psychotherapy trial, and electroconvulsive therapy (lifetime). Seventeen of the patients had a 1-month sham-controlled period and 11 patients had a 1-month open label period before the stimulation was turned on. Eight-year follow-up was available for 14 of the 28 participants. The primary outcome measure was the Illinois Density Index, which assesses the longitudinal area under the curve for behavioral measures; in this study these included response (≥50% decrease from baseline) and remission (score ≤7) on the Hamilton Depression Rating. More than 50% of patients maintained a response and 30% in remission, over the 8 years of follow-up. The physician-rated Clinical Global Impressions severity score improved from 6.1 (severely ill) at baseline to less than 3 (mildly ill or better) in this open label trial.

**Summary of Evidence**

Several case series randomized controlled trials (RCTs), and systematic reviews evaluating deep brain stimulation (DBS) in individuals with treatment-resistant depression have been published. The literature review may show that DBS may show promise for treatment-resistant depression, however, additional controlled trials are needed and should include larger and more representative samples and focus on the

identification of optimal neuroanatomical sites and stimulation parameters. The evidence is insufficient to determine that the technology results in a meaningful improvement in net health outcomes.

**Obsessive-Compulsive Disorder**
Obsessive-compulsive disorder (OCD) is a disabling and chronic psychiatric disease with an estimated lifetime prevalence of 1% to 2%. The DSM-V characterizes the main clinical symptoms of OCD by the presence of "recurrent and persistent thoughts, urges or impulses" called obsessions and by "repetitive mental or behavioral acts" named compulsions "that the individual feels driven to perform, either in response to an obsession or according to rules that must be applied rigidly". Usually, effective treatments for OCD include antidepressants and cognitive behavioral therapy (CBT). Unfortunately, 40–60% of the OCD patients do not respond to serotonin reuptake inhibitors, and about 10% remain severely affected with treatment-refractory OCD. Deep brain stimulation (DBS) has been proposed as an alternative to neurosurgical ablation in treatment-refractory OCD because it is reversible and adjustable.

**Randomized Controlled Trials**
The use of deep brain stimulation for OCD has been studied in several randomized controlled trials (RCTs), but most of them involve 10 or fewer subjects. Three studies involved larger populations: Mallet et. al. 2008; Denys et. al. 2010; and Greenberg et. al. 2010.

In 2019, Tyagi et. al. conducted randomized, double-blind, counter balanced design, investigating the efficacy of ventral capsule/ventral striatal (VC/VS) and anteromedial subthalamic nucleus (amSTN) DBS in the same patients and tested for mechanistic differences on mood and cognitive flexibility and associated neural circuitry. The possible synergistic benefit of DBS at both sites and cognitive behavioral therapy was explored. Deep brain stimulation (DBS) is an emerging treatment for severe obsessive-compulsive disorder (OCD). Six patients with treatment-refractory OCD (5 men; Yale-Brown Obsessive Compulsive Scale score >32) entered double-blind counterbalanced phases of 12-week amSTN or VC/VS DBS, followed by 12-week open phases when amSTN and VC/VS were stimulated together, in which optimal stimulation parameters were achieved and adjunctive inpatient cognitive behavioral therapy was delivered. OCD and mood were assessed with standardized scales and cognitive flexibility with the Cambridge Neuropsychological Test Automated Battery Intra-Extra Dimensional Set-Shift task. Diffusion-weighted and intraoperative magnetic resonance imaging scans were performed for tractography from optimally activated electrode contacts. DBS at each site significantly and equivalently reduced OCD symptoms with little additional gain following combined stimulation. amSTN but not VC/VS DBS significantly improved cognitive flexibility, whereas VC/VS DBS had a greater effect on mood. The VC/VS effective site was within the VC. VC DBS connected primarily to the medial orbitofrontal cortex, and amSTN DBS to the lateral orbitofrontal cortex, dorsal anterior cingulate cortex, and dorsolateral prefrontal cortex. No further improvement followed cognitive behavioral therapy, reflecting a floor effect of DBS on OCD. The authors concluded DBS

of the VC and amSTN significantly alleviated OCD symptoms, and the magnitude of effect did not differ between these sites, suggesting that both targets are equally efficacious. The finding that amSTN but not VC DBS improved cognitive flexibility and that the effect of DBS on mood was significantly greater for VC DBS implicates the involvement of different neural circuitries associated with distinct symptoms in OCD. Tractography findings revealed that VC and amSTN DBS modulate distinct brain networks implicated in OCD and are compatible with these clinical and cognitive observations. There are several limitations to the study, the main one being the small sample size. However, when comparing the efficacy of the two DBS sites, patients served as their own controls in an innovative design, and the conclusions were robust to adjustment for multiple comparisons and parametric and nonparametric analyses. Nevertheless, it would be important to test our hypothesis in a larger group of patients when the mechanistic actions of STN and VC DBS on recovery from OCD can be evaluated in more detail. Another limitation is the possible confounding effect of combined stimulation and CBT with time. Future studies could compare the effect of additional CBT at an earlier stage.

**Systematic Reviews**

Kisely et. al. (2014) undertook a systematic review and meta-analysis of the effectiveness of DBS in psychiatric conditions to maximize study power. They assessed differences in final values between the active and sham treatments for parallel-group studies and compared changes from baseline score for cross-over designs. Inclusion criteria were met by five studies, all of which were of OCD. Forty-four subjects provided data for the meta-analysis. The main outcome was a reduction in obsessive symptoms as measured by the Yale-Brown Obsessive-Compulsive Scale (YBOCS). Patients on active, as opposed to sham, treatment had a significantly lower mean score [mean difference (MD) -8.93, 95% confidence interval (CI) -13.35 to -5.76, $p < 0.001$], representing partial remission. However, one-third of patients experienced significant adverse effects (n = 16). There were no differences between the two groups in terms of other outcomes. The authors concluded DBS may show promise for treatment-resistant OCD but there are insufficient randomized controlled data for other psychiatric conditions. DBS remains an experimental treatment in adults for severe, medically refractory conditions until further data are available.

Hamani et al. (2014) conducted a systematic review of the literature and developed evidence-based guidelines on deep brain stimulation (DBS) for obsessive-compulsive disorder (OCD) that was sponsored by the American Society for Stereotactic and Functional Neurosurgery and the Congress of Neurological Surgeons (CNS) and endorsed by the CNS and American Association of Neurological Surgeons. Of 353 articles identified, 7 were retrieved for full-text review and analysis. The quality of the articles was assigned to each study and the strength of recommendation graded according to the guideline development methodology of the American Association of Neurological Surgeons/Congress of Neurological Surgeons Joint Guidelines Committee. Of the 7 studies, 1 class I and 2 class II double-blind, randomized, controlled trials reported that bilateral DBS is more effective in improving OCD symptoms than sham treatment. The

authors concluded that based on the data published in the literature, the following recommendations can be made: (1) There is Level I evidence, based on a single class I study, for the use of bilateral subthalamic nucleus DBS for the treatment of medically refractory OCD. (2) There is Level II evidence, based on a single class II study, for the use of bilateral nucleus accumbens DBS for the treatment of medically refractory OCD. (3) There is insufficient evidence to make a recommendation for the use of unilateral DBS for the treatment of medically refractory OCD. The authors noted that additional research is needed to determine which patients respond to deep brain stimulation and if specific targets may be more suitable to treat a specific set of symptoms.

A meta-analysis by Alonso et. al. (2015) included studies of any type (including case reports) evaluating deep brain stimulation (DBS) for obsessive compulsive disorder (OCD) and reporting changes in Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score. Reviewers identified 31 studies (total N=116 patients). They did not report study type (i,e,, 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 subthalamic nucleus (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 (i.e., >35% reduction in post-treatment 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.

In a systematic review, Naesstrom et al. (2016) reviewed the current studies on psychiatric indications for deep brain stimulation (DBS), with focus on obsessive-compulsive disorder (OCD) and major depressive disorder (MDD). A total of 52 studies met the inclusion criteria with a total of 286 unique patients treated with DBS for psychiatric indications; 18 studies described 112 patients treated with DBS for OCD in six different anatomical targets, while nine studies included 100 patients with DBS for MDD in five different targets. The authors concluded that DBS may show promise for treatment-resistant OCD and MDD, but the results are limited by small sample size and insufficient randomized controlled data. According to the authors, other psychiatric indications are currently of a purely experimental nature.

In a systematic review, Vazquez-Bourgon et al. (2017) evaluated the current scientific evidence on the effectiveness and applicability of deep brain stimulation (DBS) for refractory obsessive-compulsive disorder (OCD). The critical analysis of the evidence shows that the use of DBS in treatment-resistant OCD is providing satisfactory results regarding efficacy, with assumable side-effects. However, there is insufficient evidence to support the use of any single brain target over another. The authors concluded that the use of DBS for OCD is still considered to be in the field of research, although it is

increasingly used in refractory-OCD, producing in the majority of studies significant improvements in symptomatology, and in functionality and quality of life. According to the authors, it is important to implement random and controlled studies regarding its long-term efficacy, cost-risk analyses, and cost/benefit.

In 2019, Tastevin et. al. reported on the current perspectives of deep brain stimulation (DBS) in treatment-refractory obsessive-compulsive disorder (OCD). Several studies and recent meta-analysis using functional and structural neuroimaging highlighted abnormal activity and neuroanatomical abnormalities in cortico-striato-thalamo-cortical (CSTC) circuits in patients with OCD (including the orbitofrontal cortex (OFC), the anterior cingulate cortex (ACC), prefrontal cortex (PFC) and the ventral striatum). Interestingly, the main hypothesis is that OCD is associated with hyperactivity of the CSTC loop. Even if the mechanism of DBS is still unknown, the possibility of its therapeutic effects could be explained by a global inhibition of this network. Two main stimulation areas have been widely studied. First, the striatal region includes the anterior limb of the internal capsule (ALIC), the ventral striatum/ventral capsule (VS/VC), the nucleus accumbens (NAc), the bed nucleus of the striata terminalis (BST), the ventral caudate nucleus, the medial forebrain bundle (MFB). The second main area is the subthalamic nucleus (STN). All clinical trials used Y-BOCS (The Yale-Brown Obsessive-Compulsive Scale) as the main outcome measure. Clinical trials involving DBS responders are mostly defined as a 25–35% reduction in YBOCS. Based on review of randomized controlled trials the authors concluded DBS cannot be currently considered as an established therapy for OCD.

In 2020, Raviv et. al. completed a systematic review of deep brain stimulation (DBS) targets for obsessive compulsive disorder (OCD). Selected publications included 9 randomized controlled trials, 1 cohort study, 1 case-control study, 1 cross-sectional study, and 16 case series. Striatal region targets such as the anterior limb of the internal capsule, ventral capsule/ventral striatum, and nucleus accumbens were identified, but stereotactic coordinates were similar despite differing structural names. Only 15 of 28 articles included coordinates. The authors concluded the striatal area is the most targeted region for OCD-DBS. We recommend a common nomenclature based on this review. To move the field forward to individualized therapy, active contact location relative to stereotactic coordinates and patient specific anatomical and clinical variances need to be reported.

In 2021, Bouwens van der Vlis et.al. conducted a systematic review to evaluate the cognitive outcome following deep brain stimulation (DBS) for refractory obsessive-compulsive disorder (OCD). Fifteen studies (n=178) consisting of five randomized controlled crossover studies, five observational studies, one pilot study, two case series, and two case reports (n=1-24) were included. Primary outcomes were cognitive outcomes measured by any neuropsychological assessment. A total of 37 neuropsychological tests were used within the 15 studies reporting on cognitive outcome following DBS for OCD. Variable outcomes of DBS were observed in the domains of attention, memory, executive functioning, and in particular cognitive flexibility. Author noted limitations included

heterogeneity in study design, stimulation targets, variable data presentation and diversity of neuropsychological tests.

Hayes Technology Assessment published August 2020 and last reviewed September 2021 on the use of deep brain stimulation (DBS) for the treatment of refractory obsessive-compulsive disorder (OCD) that found the overall evidence on the safety and effectiveness of DBS for refractory OCD very low. Additional studies are needed with consistent reporting on outcome measures and long-term follow-up would assist in determining whether DBS offers any sustained benefit to individuals with refractory OCD. Studies should also compare DBS with clinical alternatives to determine whether DBS is a viable treatment option.

**Summary of Evidence**
The literature on deep brain stimulation (DBS) for obsessive-compulsive disorder (OCD) consists of randomized controlled trials (RCTs), several uncontrolled studies and systematic reviews. Based on review of the literature for deep brain stimulation (DBS) in treatment-refractory obsessive-compulsive disorder (OCD) this may show promise, but the results are limited by small sample size and insufficient randomized controlled data. Additional randomized controlled studies are needed to determine which patients respond to deep brain stimulation (DBS) and if specific targets may be more suitable to treat a specific set of symptoms and to determine the long-term efficacy. The evidence is insufficient to determine that the technology results in a meaningful improvement in net health outcome.

On February 19, 2009, the Reclaim device (Metronic Neuro, Minneapolis, MN) received FDA approval under the Humanitarian Devices Exemption (HDE) process. The FDA labeling states that the device is indicated for bilateral stimulation of the anterior limb of the internal capsule (AIC), as an adjunct to medications and as an alternative to anterior capsulotomy for treatment of chronic, severe, treatment-resistant OCD in adults who have failed at least three selective serotonin reuptake inhibitors (SSRIs). *See medical policy 10.01.14 Humanitarian Use Devices.*

**Tourette Syndrome**
Tourette syndrome (TS) is a neurological disorder characterized by repetitive, stereotyped, involuntary movements and vocalizations called tics. The early symptoms of TS are typically noticed first in childhood, with the average onset of ages 3 and 9 years. TS occurs in people from all ethnic groups and males are affected about three to four times more often than females. It is estimated that 200,000 Americans have the most severe form of TS, and as many as one in 100 exhibit milder and less complex symptoms such as chronic motor or vocal tics. Although TS can be a chronic condition with symptoms lasting a lifetime, most people with the condition experience their worst tic symptoms in their early teens, with improvement occurring in the late teens and continuing into adulthood.

Tics are classified as either simple or complex. Simple motor tics are sudden, brief, repetitive movements that involve a limited number of muscle groups. Some of the more common simple tics include eye blinking and other eye movements, facial grimacing, shoulder shrugging, and head or shoulder jerking. Simple vocalization might include repetitive throat clearing, sniffing, or grunting sounds. Complex tics are distinct, coordinated patterns of movements involving several muscle groups. Complex motor tics might include facial grimacing combined with a head twist and shoulder shrug. Other complex motor tics may appear purposeful, including sniffing, or touching objects, hopping, jumping, bending, or twisting. Simple vocal tics may include throat-clearing, sniffing/snorting, grunting, or barking. More complex vocal tics include words or phrases. The most dramatic and disabling tics include motor movements that result in self-harm such as punching oneself in the face or vocal tics including coprolalia (uttering socially inappropriate words such as swearing) or echolalia (repeating words or phrases of others). Tics are often work with excitement or anxiety and better during calm, focused activities. Tics do not go away during sleep but are often significantly diminished.

Because tic symptoms often do not cause impairment, the majority of individuals with TS require no medication for tic suppression. However, effective medications are available for those whole symptoms interfere with functioning. Neuroleptics (drugs that may be used to treat psychotic and non-psychotic disorders) are the most consistently useful medications for tic suppression; a number are available, but some are more effective than others such as haloperidol and pimozide. Behavioral treatments such awareness training and competing response training can also be used to reduce tics. Deep brain stimulation has been studied in the treatment of TS.

Several systematic reviews of the literature on DBS for Tourette syndrome have been published.

In 2021, Wehmeyer et. al. also conducted a pooled analysis. A total of 65 studies with 376 patients were included; the primary outcome was YGTSS scores, and scores were significantly reduced at maximum follow-up of median 25 months ($p<.001$). The median scores decreased from 79.92 points (interquartile range [IQR], 13.25) to 34.69 points (IQR, 20.93) post-surgery, which represented a reduction rate of 56.59%. A majority of patients (69.4%) also experienced symptom reduction of more than 50% at maximum follow-up. In addition, other tic-related outcome measures (modified Rush video-based tic rating scale, YGTSS total tic score) and comorbidities (Yale-Brown Obsessive Compulsive Scale, Becks Depression Inventory), were also significantly reduced after deep brain stimulation.

A systematic review by Piedad et. al. examined patient and target selection for use of deep brain stimulation (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 subthalamic nucleus (STN), caudate nucleus, globus pallidus internus (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.

Most recent systematic reviews (i.e., 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 deep brain stimulation (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 globus pallidus (GPi) anteromedial part (n=44) and post ventrolateral part (n=20). Two of the RCTs used thalamic stimulation, one used bilateral globus pallidus (GPi) 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). The authors concluded despite small patient numbers; we conclude that DBS for GTS is a valid option for medically intractable patients. Different brain targets resulted in comparable improvement rates, indicating a modulation of a common network. Future studies might focus on a better characterization of the clinical effects of distinct regions, rather than searching for a unique target.

**Randomized Controlled Trials (RCTs)**
The crossover randomized controlled trial (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 globus pallidus (GPi) surgery for deep brain stimulation (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 Yale Global Tic Severity Scale (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.

In a randomized, double-blind, controlled trial, Welter et al. (2017) assessed the efficacy of anterior internal globus pallidus (aGPi) DBS for severe Tourette's syndrome. The

study included patients aged 18-60 years with severe and medically refractory Tourette's syndrome from eight hospitals specialized in movement disorders. Enrolled patients received surgery to implant bilateral electrodes for aGPi DBS; 3 months later they were randomly assigned (1:1 ratio with a block size of eight; computer-generated pairwise randomization according to order of enrolment) to receive either active or sham stimulation for the subsequent 3 months in a double-blind fashion. All patients then received open-label active stimulation for the subsequent 6 months. Patients and clinicians assessing outcomes were masked to treatment allocation; an unmasked clinician was responsible for stimulation parameter programming, with intensity set below the side-effect threshold. Nineteen patients were enrolled in the trial. The investigators randomly assigned 17 (89%) patients, with 16 completing blinded assessments (seven [44%] in the active stimulation group and nine [56%] in the sham stimulation group). There was no significant difference in YGTSS score change between the beginning and the end of the 3-month double-blind period between groups. During the following 6 month open-label period, stimulation decreased motor and vocal tic severity, with evidence of an improvement in occupational activities and life satisfaction. Fifteen serious adverse events were reported in 13 patients, of which eight events were related to the surgical procedure or hardware. According to the authors, future research is needed to investigate the efficacy of aGPi DBS for patients over longer periods with optimal stimulation parameters and to identify potential predictors of the therapeutic response.

Martinez-Ramirez et al. (2018) assessed the efficacy and safety of deep brain stimulation (DBS) in a multinational cohort of patients with Tourette syndrome using the International Deep Brain Stimulation Database and Registry. The registry included 185 patients with medically refractory Tourette syndrome who underwent DBS implantation from January 1, 2012, to December 31, 2016, at 31 institutions in 10 countries worldwide. These patients received DBS implantation in different regions of the brain depending on their symptoms. The mean (SD) total Yale Global Tic Severity Scale score improved from 75.01 (18.36) at baseline to 41.19 (20.00) at 1 year after DBS implantation. The mean (SD) motor tic subscore improved from 21.00 (3.72) at baseline to 12.91 (5.78) after 1 year, and the mean (SD) phonic tic subscore improved from 16.82 (6.56) at baseline to 9.63 (6.99) at 1 year. The overall adverse event rate was 35.4% (56 of 158 patients. The most common stimulation-induced adverse effects were dysarthria (10 [6.3%]) and paresthesia (13 [8.2%]). The authors concluded that deep brain stimulation was associated with symptomatic improvement in patients with Tourette syndrome but also with important adverse events. Long-term assessments will be necessary to monitor adverse effects and determine if DBS has lasting effects on symptoms.

**Summary of Evidence**

A number of uncontrolled studies randomized controlled trials (RCTs), and several systematic reviews have been published. Most studies, including the RCTs had small sample sizes and used a variety of DBS targets. A 2015 meta-analysis suggested that DBS might improve outcomes in patients with Tourette syndrome (TS). However, there

is limited information from randomized clinical trials for analysis and interpretation. There is no consensus on the optimal brain target for the treatment of tics, but the following regions have been stimulated in individuals with TS: the centromedian thalamus, the globus pallidus internus (ventral and dorsal), the globus pallidus externus, the subthalamic nucleus, and the ventral striatum/ventral capsular nucleus accumbens region. DBS of the anteromedial globus pallidus is probably more likely than sham stimulation to reduce tic severity (EVID). There is insufficient evidence to determine the efficacy of DBS of the thalamus or the centromedian-parafascicular complex region of the thalamus in reducing tic severity (EVID). Complications of treatment, including infection and removal of hardware, appear more common with TS (EVID) than with other neurologic conditions. Further randomized controlled studies in larger numbers of individuals are needed. The evidence is insufficient to determine that the technology results in a meaningful improvement in net health outcome.

**Drug Addiction**

Drug addiction represents a significant public health concern that has high rates of relapse despite optimal medical therapy and rehabilitation support. New therapies are needed, and deep brain stimulation (DBS) is being studied for the treatment of drug addiction.

In 2018, Wang et. al. reviewed deep brain stimulation for the treatment of drug addiction. The most common target for stimulation has been the nucleus accumbens, a key structure in the mesolimbic reward pathway. In addiction the mesolimbic reward pathway undergoes a series of neuroplastic changes. Chief among them is a relative hypofunctioning of the prefrontal cortex, which is thought to lead to the diminished impulse control that is characteristic of drug addiction. The prefrontal cortex, as well as other targets involved in drug addiction such as the lateral habenula, hypothalamus, insula, and subthalamic nucleus have also been stimulated in animals, with encouraging results.

**Summary of Evidence**

The published studies for DBS for drug addiction is currently limited to several promising case series or case reports that are not controlled. Further studies are needed to determine what role DBS can play in the treatment of drug addiction. The evidence is insufficient to determine that the technology results in a meaningful improvement in net health outcome.

**Other Indications**

Deep brain stimulation (DBS) has also been investigated for other disorders including but not limited to the following: appetite disorders such as anorexia nervosa and refractory obesity, Alzheimer disease/dementias, head or voice tremor, Huntington’s disease, traumatic brain injury (TBI), impulsive or violent behavior and chronic pain. The studies investigating DBS for the treatment of these other conditions are mainly trials with small sample sizes and short-term follow-up. Further well-designed studies are needed to demonstrate benefits of deep brain stimulation (DBS) for these disorders to include

stimulation parameters and identify robust predictors of patient response. The evidence is insufficient to determine that the technology results in a meaningful improvement in net health outcomes.

**Primary Dystonia**

**Clinical Context and Therapy Purpose**
Deep brain stimulation (DBS) has also been investigated in individuals with primary 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.

Deep brain stimulation (DBS) for the treatment of primary dystonia received Food and Drug Administration (FDA) approval through the humanitarian device exemption process in 2003. The humanitarian device exemption 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.

**Populations**
The relevant population(s) of interest are individuals with primary or secondary dystonia. Primary dystonia is defined when dystonia is the only symptom unassociated with other pathology. 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.

**Interventions**
The therapy being considered is deep brain stimulation (DBS).

**Comparators**
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.

As noted in the FDA humanitarian device exemption analysis of risk and probable benefit, the only other treatment options for chronic refractory primary dystonia are neurodestructive procedures. DBS provides a reversible alternative.

**Outcomes**
Efficacy outcomes include clinical severity of dystonia and disability by combining the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) or Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) and quality of life (QOL)

The Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) total score ranges from 0 to 150. It has 2 subscales: a movement sub-scale, based on clinical patient examination, that assesses dystonia severity and provoking factors in different body areas, with a maximum score of 120; and a disability sub-scale, that evaluates the patients' report of disability in activities of daily living, for a maximum score of 30. Higher scores correspond to greater levels of morbidity. There is currently no established minimally important difference in the BFMDRS total score.

Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) is most used to assess the status of people with cervical dystonia. The TWSTRS has a total score ranging from 0 to 85. It is a composite of 3 sub-scales: severity which ranges from 0 to 35; disability which ranges from 0 to 30; and pain which ranges from 0 to 20. Higher scores correspond to greater levels of morbidity.

**Systematic Reviews**
Moro et. al. (2017) published a systematic review and meta-analysis, and the aim of this review was to provide strong clinical evidence of the efficacy of deep brain stimulation for the globus pallidus internus (GPi) in 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 above) 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.

**Randomized Controlled Trials (RCTs)**
The randomized controlled trial (RCT), which was industry sponsored, patient- and observer-blinded evaluation of pallidal neurostimulation in subjects with refractory cervical dystonia, was published by Volkmann et. al. (2014). The trial included 62 adults with cervical dystonia for 3 or more years in duration, a severity score of 15 or more 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 group 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 (i.e., slightly slurred speech), which was not reversible in 6 patients. The authors concluded pallidal neurostimulation for 3 months is more effective than sham stimulation at reducing symptoms of cervical dystonia. Extended follow-up is needed to ascertain the magnitude and stability of chronic neurostimulation effects before this treatment can be recommended as routine for patients who are not responding to conventional medical therapy.

**Summary of Evidence**
A review prepared for the Food and Drug Administration (FDA) and a 2017 systematic review have evaluated evidence on deep brain stimulation (DBS) for primary dystonia. There are numerous small case series and a randomized controlled trial (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).

Deep brain stimulation (DBS) for the treatment of primary dystonia received Food and Drug Administration (FDA) approval through the humanitarian device exemption process in 2003. See also medical policy 10.01.14 Humanitarian Use Devices.

**Cluster Headaches and Facial Pain**

**Clinical Context and Therapy Purpose**
The purpose of deep brain stimulation is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with cluster

headache or facial pain. Deep brain stimulation (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.

**Populations**
The relevant population of interest are individuals with cluster headache or facial pain. The International Headache Society's International Classification of Headache Disorders classifies types of primary and secondary headaches. A summary of cluster headache based on the International Classification of Headache Disorders criteria is below:

Cluster headaches are primary headaches classified as trigeminalautomomiccephalgias that can be either episodic or chronic. The diagnostic criteria for cluster headaches states that these are attacks of severe, unilateral orbital, supraorbital, and/or temporal pain that lasts 15-180 minutes and occurs from once every other day to 8 times a day and further requires for the patient to have had at least 5 such attacks with at least 1 of the following signs or symptoms, ipsilateral to the headache: conjunctival injection and/or lacrimation; nasal congestion and/or rhinorrhea; eyelid edema; forehead and facial sweating; miosis and/or ptosis; or a sense of restlessness or agitation. The diagnostic criteria for episodic cluster headache require at least two cluster periods lasting from seven days to one year if untreated and separated by pain free remission periods of $\geq$ 3 months. The diagnostic criteria for chronic cluster headache require cluster headaches occurring for one year or more without remission, or with remission of less than three months. The age at onset for cluster headaches is generally 20-40 years and men are affected three times more often than are women.

**Interventions**
The therapy being considered is deep brain stimulation (DBS).

**Comparators**
The following practice is currently being used to treat cluster headache and facial pain: pharmacologic therapy, botulinum toxin, or conservative therapy (e.g., diet, exercise). The standard of care treatment to stop or prevent attacks of cluster headache or migraine is medical therapy. Guideline recommended treatments for acute cluster headache attaches include oxygen inhalation and triptans (e.g., sumatriptan and zolmitriptan). Oxygen is preferred first-line, if available, because there are no documented adverse effects for most adults. Triptans have been associated with primarily nonserious adverse events; some patients experience non-ischemic chest pain and distal paresthesia. Use of oxygen may be limited by practical considerations and the FDA approved labeling for subcutaneous sumatriptan limits use to two doses per day. Steroid injections may be used to prevent or reduce the frequency of cluster headaches. Verapamil is also frequently used for prophylaxis although the best evidence supporting its effectiveness is a placebo controlled RCT including 30 patients.

Given the high placebo response rate in cluster headaches, trials with sham DBS are relevant.

**Outcomes**
The general outcomes of interest are headache intensity and frequency, the effect on function and quality of life (QOL) and adverse events.

The most common outcome measures for prevention of cluster headache are decrease in headache days per month compared with baseline and the proportion of responders to the treatment, defined as those individuals who report more than a 50%, 75% or 100% decrease in headache days per month compared to pre-treatment.

Safety outcomes include death, stroke, depression, cognition, infection and other device and procedure related events.

**Randomized Controlled Trials (RCTs)**
Fontaine et. al. published the results of a prospective crossover, double-blind, multicenter study assessing the efficacy and safety of unilateral hypothalamic deep brain stimulation (DBS) in 11 patients with refractory chronic cluster headache (CCH). The randomized phase compared active and sham stimulation during 1-month periods and was followed by a 1-year open phase. The severity of CCH was assessed by the weekly attacks frequency (primary outcome), pain intensity, sumatriptan injections, emotional impact (HAD) and quality of life. Tolerance was assessed by active surveillance of behavior, homeostatic and hormonal functions. 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, 6/11 responded to the chronic stimulation (weekly frequency of attacks decrease [50%]), including three pain-free patients. There were three serious adverse events, including subcutaneous infection, transient loss of consciousness and micturition syncope. No significant change in hormonal functions or electrolytic balance was observed. Randomized phase findings of this study did not support the efficacy of DBS in refractory CCH, but open phase findings suggested long-term efficacy in more than 50% patients, confirming previous data, without high morbidity. Discrepancy between these findings justifies additional controlled studies.

Seiijo-Fernandez et. al. 2018, deep brain stimulation (DBS) and the proper target for cluster headache (CCH) are still a subject of controversy. The objective of this study was to present long-term results of analysis of the target and its structural connectivity. Fifteen patients with drug resistant CCH underwent DBS in coordinates 4 mm lateral to the III ventricular wall and 2 mm behind and 5 mm below the intercommissural point. The clinical parameters recorded were the number of weekly attacks, pain intensity, and duration of the headache. Structural connectivity was studied using 3-T MR diffusion tensor imaging (DTI). All of the patients improved from a mean of 39 attacks/week to 2; pain intensity decreased from 9 to 3 out of 10, and the man cephalgia duration decreased from 53 to 8 minutes. The mean stereotactic coordinates of the effective contact location were 6.1 mm lateral to the midcommissural point and 1.2 mm behind and 4.0 mm below the intercommissural point. DTI analysis showed that this target was connected to tracts and nuclei of the posterior-mesencephalic tegmentum, specifically the dorsal longitudinal

and mamillotegmental fasciculi. The authors concluded, the data showed DBS to be a safe and useful procedure for the treatment of drug-resistant CCH as the rate of improvement was higher than those found in other series. Although these are promising results, larger series targeting those fasciculi with a longer follow-up are needed.

**Observational Study**
In 2020, Albar-Duran et. al. reported on two prospective cohorts of patients with refractory cluster headaches (CCH) treated with occipital nerve stimulation (ONS) and deep brain stimulation (DBS) and compared preoperative to postoperative status at 6 and 12 months after the surgery and at final follow-up. There is little literature regarding the long-term follow-up of these treatments. Efficacy analysis included medication reduction and complications. The ONS group consisted for 13 men and 4 women, with a median age of 44 years (range 31-61 years). The median number of attacks per week before surgery was 28 (range 7-70), and the median follow-up duration was 48 months. The DBS group comprised 5 men and 2 women, with a median age of 50 years (range 29-64 years), The median number of attacks before surgery was 56 (range 14-140), and the median follow-up was 36 months. The number of attacks per week and visual analog scale sore were significantly reduced for the ONS and DBS groups after surgery. However, while all the patients from the DBS group were considered responders at final follow-up, with more than 85% being satisfied with the treatment, approximately 29% of initial responders to ONS became resistant by the final follow-up ($p=0.0253$). The authors concluded ONS is initially effective as a treatment for refractory cluster headaches, although a trend toward loss of efficacy was observed. No clear predictors of good clinical response were found in the present study. Conversely, DBS appears to be effective and provide a more stable clinical response over time with an acceptable rate of surgical complications.

**Case Series**
Two case series were published on use of deep brain stimulation (DBS) for the ipsilateral posterior hypothalamus in patients with cluster headaches and atypical facial pain and DBS in craniofacial pain. 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.

**Summary of Evidence**
Case series, observational studies, and randomized controlled trials (RCTs) have been published on the use of deep brain stimulation for treatment of refractory cluster headaches or facial pain. Deep brain stimulation (DBS) and the proper target for cluster headache (CCH) are still a subject of controversy and there is little literature regarding the long-term follow-up of this treatment. One randomized controlled trial (RCT) may have shown some promise however, another RCT that included 11 patients showed there were no significant differences between groups receiving active and sham stimulation. Additional RCTs are needed with larger sample sizes and longer follow-up to determine the safety and efficacy of DBS for the treatment of refractory cluster headaches. The

evidence is insufficient to determine that the technology results in a meaningful improvement in net health outcomes.

**Practice Guidelines and Position Statements**

**American Academy of Neurology (AAN)**
In 2011, the American Academy of Neurology (AAN) published an updated guideline on the treatment of essential tremor (ET). There were no changes from the conclusions and recommendations of the 2005 practice parameters regarding DBS for ET. The guidelines stated bilateral DBS of the thalamic nucleus may be used to treat medically refractory limb tremor in both upper limbs (level C possibly effective), but there were insufficient data regarding the risk/benefit ratio of bilateral versus unilateral DBS in the treatment of limb tremor. There was insufficient evidence to make recommendation regarding the use of thalamic for head or voice tremor (Level U, treatment is unproven) (This guideline was reaffirmed on April 30, 2014)

In 2013, the American Academy of Neurology (AAN) published an evidence- based guideline on the treatment of tardive syndromes which indicated: The available evidence which consists of class IV studies comprising of case reports or small case series, is insufficient to support or refute pallidal deep brain stimulation (DBS) for tardive syndromes. (This guideline was reaffirmed on July 16, 2016)

In 2019, the American Academy of Neurology (AAN) published a practice guideline on the treatment of tics in people with Tourette syndrome and chronic tic disorders which includes the following recommendations regarding deep brain stimulation (DBS):

- Physicians must use a multidisciplinary evaluation (psychiatrist or neurologist, neurosurgeon, and neuropsycholollgist) to establish when the benefits of treatment outweigh the risk for prescribing DBS for medication-resistant motor and phonic tics. (Level A)
- Physicians should confirm the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnosis of TS and exclude secondary and functional tic-like movements when considering DBS for medication-resistant tics. (Level B)
- A mental health professional must screen patients preoperatively and follow patients postoperatively for psychiatric disorders that may impeded the long-term success of the therapy. (Level A)
- Physicians must confirm that multiple classes of medication (antipsychotics, dopamine depleters, alpha-1 agonists) and behavioral therapy have been administered (or contraindicated) before prescribing DBS for tics. (Level A)
- Physicians may consider DBS for severe, self-injurious tics, such as severe cervical tics that result in spinal injury. (Level C)

**Rationale**
Patients with severe Tourette syndrome (TS), resistant to medical and behavioral therapy, may benefit from the application of deep brain stimulation (DBS). An important

challenge and limitation in the evaluation of the evidence around DBS in TS is that, even in expert DBS centers, few operations per year are performed. Furthermore, there is limited information from randomized clinical trials for analysis and interpretation. There is no consensus on the optimal brain target for the treatment of tics, but the following regions have been stimulated in patients with TS: the centromedian thalamus, the globus pallidus internus (ventral and dorsal), the globus pallidus externus, the subthalamic nucleus, and the ventral straitum/ventral capsular nucleus accumbens region. DBS of the anteromedial globus pallidus is possibly more likely than sham stimulation to reduce tic severity. There is insufficient evidence to determine the efficacy of DBS of the thalamus or the centromedian-parafascicular complex region of the thalamus in reducing tic severity. Complications of treatment, including infection and removal of hardware, appear more common with TS than with other neurologic conditions.

Recommendations from the Movement Disorders Society suggest that, when DBS is used in TS, best practices used for other DBS applications are followed, including confirmation of diagnosis, use of multidisciplinary screening, and stabilization of psychiatric comorbidities including of active suicidality. Appropriate patient selection is one of the most important predictors of success of DBS treatment, making multidisciplinary evaluation essential. Because of the complexity of the patient population, centers performing DBS have been encouraged to screen candidates preoperatively and to follow them postoperatively. There has been concern about high risk of suicide and other negative psychiatric sequelae in patients with TS not screened and monitored for depression, anxiety and bipolar tendencies. The largest available randomized trials for DBS have revealed benefits on motor and phonic tics for the ventral globus pallidus internus and the centromedian thalamic region target; however, these studies have raised methodologic concerns that need to be addressed in future trials. There is little information on the effects of DBS on psychiatric comorbidities and the efficacy of DBS in children with TS.

**American Association of Neurological Surgeons (AANS)**
In 2018, the Congress of Neurological Surgeons (AANS) published a systematic review and evidence-based guideline on subthalamic nucleus and globus pallidus internus deep brain stimulation for the treatment of patients with Parkinson's disease: executive summary that included the following recommendations:

- Given that bilateral STN DBS is at least as effective as bilateral GPi DBS in treating motor symptoms of Parkinson's disease (as measured by improvements in UPDRS-III scores), consideration can be given to the selection of either target in patients undergoing surgery to treat motor symptoms. (Level I)
- When the main goal of surgery is reduction of dopaminergic medications in a patient with Parkinson's disease, then bilateral STN DBS should be performed instead of GPi DBS. (Level I)
- There is insufficient evidence to make a generalizable recommendation regarding the target selection for reduction of dyskinesias. However, when the reduction of medication is not anticipated and there is a goal to reduce the severity of "on" medication dyskinesias, the GPi should be targeted. (Level I)

- When considering improvements in quality of life in a patient undergoing DBS for Parkinson's disease, there is no basis to recommend bilateral DBS in 1 target over the other. (Level I)
- If there is significant concern about cognitive decline, particularly in regards to processing speed and working memory in a patient undergoing DBS, then the clinician should consider using GPi DBS rather than STN DBS, while taking into consideration other goals of surgery. (Level I)
- If there is significant concern about the risk of depression in a patient undergoing DBS, then the clinician should consider using pallidal rather than STN stimulation, while taking into consideration other goals of surgery. (Level I)
- There is insufficient evidence to recommend bilateral DBS in 1 target over the other in order to minimize the risk of surgical adverse events.

**American Psychiatric Association**
In 2010, the American Psychiatric Association guideline on the treatment of major depressive disorder and the 2014 guideline watch, did not mention the use of deep brain stimulation (DBS) for the treatment of major depressive disorder.

**National Institute of Health and Care Excellence (NICE)**
The National Institute of Health and Care Excellence (NICE) has published Interventional Procedure Guidance documents on deep brain stimulation (DBS):

**Parkinson's Disease**:
In 2017, NICE guideline (NG71) states the following:
- Do not offer deep brain stimulation to people with Parkinson's disease whose symptoms are adequately controlled by best medical therapy.
- Consider deep brain stimulation for people with advanced Parkinson's disease whose symptoms are not adequately controlled by best medical therapy.

**Regulatory Status**
In 1997, the Activa® Tremor Control System, manufactured by Medtronic Corp, MN, was cleared for marketing by the 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. While the original 1997 FDA-labeled indications were limited to unilateral implantation of the device for the treatment of tremor, in January 2002, the FDA-labeled indications were expanded to include bilateral implantation as a treatment to decrease the symptoms of advanced Parkinson's disease that are not controlled by medication.

In April 2003, the FDA labeled indications for the Activa® Tremor Control System, manufactured by Medtronic Corp, MN for deep brain stimulation were 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 received FDA approval through the Humanitarian Device Exemption process.

In 2017 the FDA labeled indications for the Activa® Tremor Control System, manufactured by Medtronic Corp, MN for deep brain stimulation regarding Parkinson's disease was 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 February 2009, the FDA approved deep brain stimulation with the Reclaim® device (Medtronic, Inc.) via the Humanitarian Device Exemption (HDE) process for the treatment of severe treatment resistant obsessive-compulsive disorder (OCD). This device is indicated for bilateral stimulation of the anterior limb of the internal capsule, AIC, as an adjunct to medication and as an alternative to anterior capsulotomy for the treatment of chronic, severe treatment resistant obsessive-compulsive disorder (OCD) in adult patients who have failed at least three selective serotonin reuptake inhibitors (SSRIs).

In June 2015, the FDA approved the Brio Neurostimulation System (now called Infinity; St. Jude Medical Neuromodulation) as a PMA (premarket approval) device for the following indications: 1) bilateral stimulation of the subthalmic nucleus (STN) as an adjunctive therapy to reduce some of the symptoms of advanced levodopa-responsive Parkinson's disease (PD) that are not adequately controlled by medications; 2) unilateral or bilateral stimulation of the ventral intermediate (VIM) of the thalamus for the suppression of disabling upper extremity tremor in adult essential tremor patients whose tremor is not adequately controlled by medications and where the tremor constitutes a significant functional disability. This is a rechargeable system.

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.

In 2018, the FDA approved the Medtronic DBS System for Epilepsy (Medtronic, Inc) through the Premarket Approval process. The pivotal study was the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy. The intended use is bilateral stimulation of the anterior nucleus of the thalamus as an adjunctive therapy for reducing the frequency of seizures in individuals 18 years of age or older diagnosed with epilepsy characterized by partial-onset seizures, with or without secondary generalization, that are refractory to three or more anti-epileptic medications.

In 2020, the FDA approved the Percept PC Deep Brain Stimulation (Boston Scientific) which records brain signals while delivering therapy for Parkinson's disease (PD).

In 2021, the FDA approved the Vercise Genus Deep Brain Stimulation System (Boston Scientific) which provides stimulation of the subthalamic nucleus and globus pallidus for Parkinson's disease (PD).

In 2021, the FDA approved the SenSight Directional Lead System which provides unilateral and bilateral stimulation for Parkinson's disease (PD), tremor, dystonia and epilepsy.

# PRIOR APPROVAL

Not applicable.

# POLICY

**See Related Medical Policies**

- 10.01.14 Humanitarian Use Devices
- 07.01.71 Responsive Neurostimulation for the Treatment of Refractory Focal Epilepsy
- 07.01.60 Vagus Nerve Stimulation (VNS) and Vagal Nerve Blocking Therapy

**Primary Dystonia**

Unilateral or bilateral deep brain stimulation (DBS) of the globus pallidus (GPi) or the subthalmic nucleus (STN) may be considered **medically necessary** in individuals 7 years of age or older with chronic intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia and cervical dystonia (torticollis).

**Parkinson's Disease and Essential Tremor**

Unilateral or bilateral deep brain stimulation (DBS) of the globus pallidus (GPi) or subthalmic nucleus (STN) may be considered **medically necessary** for an individual with Parkinson's disease (PD) and meet **ALL** the following criteria:

- A good response previously to levodopa or other pharmacologic therapy for the treatment of Parkinson's disease (PD) but is now medically refractory (motor complications not controlled by pharmacologic therapy); **and**
- One of the following:
    - A minimum score of 30 points on the motor portion of the United Parkinson Disease Rating Scale when the patient has been without medication for approximately 12 hours; **or**
    - Parkinson disease (PD) for at least 4 years.

Unilateral deep brain stimulation (DBS) of the thalamus may be considered **medically necessary** in individuals with disabling, medically unresponsive tremor due to essential tremor (ET) or Parkinson's disease (PD).

Bilateral deep brain stimulation of the thalamus may be considered **medically necessary** in individuals with disabling, medically unresponsive tremor in both upper limbs due to essential tremor (ET) or Parkinson's disease (PD).

**Note:** Disabling, medically unresponsive tremor is defined as the following:

- Tremor causing significant limitation in daily activities
- Inadequate control by maximal dosage of medication for at least 3 months before implant.

**Medically Refractory Epilepsy**

Deep brain stimulation (DBS) of the anterior nucleus of thalamus may be considered **medically necessary** for an individual with medically refractory epilepsy using the Medtronic DBS System for Epilepsy who meet **ALL** the following criteria:

- 18 years of age or older; **and**
- Having focal (partial onset) seizures with or without secondary generalized seizures; **and**
- Is medically refractory (failed) at least 3 antiepileptic drugs (AEDs); **and**
- The individual is currently averaging 6 or more focal (partial onset) seizures per month with no more than 30 days between seizures with current antiepileptic drug(s) (AEDs); **and**
- Are not a candidate for resective epilepsy surgery or has failed resective epilepsy surgery; **and**
- If the individual currently has a vagus nerve stimulation (VNS) device, they are agreeable to the device being turned off and the generator removed prior to the deep brain stimulation device/generator being implanted; **and**
- The individual does not have the following:
    - Diagnosis or evidence of a neurological disorder or condition affecting the brain likely to progress (e.g., brain tumor, active encephalitis, active meningitis or abscess, arteriovenous malformations or cavernous angiomas that are likely to progress).

**Replacement or Revision of Deep Brain Stimulator (DBS)**

Replacement or revision of deep brain stimulator (DBS) generator and/or lead/electrode(s) and/or programmer may be considered **medically necessary** for an individual that meets the above medical necessity criteria and the existing generator/lead/electrode(s)/programmer is no longer under warranty and cannot be repaired.

**Investigational**

Deep brain Stimulation (DBS) is considered **investigational** for all other indications, including but not limited to the following because the safety and effectiveness of deep

brain stimulation (DBS) cannot be established by review of the available published peer-reviewed literature. More large scale randomized controlled trials with larger number of individuals are needed to explore different stimulation parameters, re-evaluate the indications for deep brain stimulation (DBS) and identify robust predictors of individual response. The evidence is insufficient to determine the effects of this technology on net health outcomes:

- Indications not meeting the above medical necessity criteria
- Depression/treatment resistant depression
- Alzheimer's Disease/dementias
- Chronic pain/Chronic pain syndromes
- Obsessive-compulsive disorder (OCD): ***Note****: For deep brain stimulation using the Reclaim device for the treatment of severe treatment resistant obsessive-compulsive disorder (OCD) in an adult individual see Medical Policy 10.01.14 Humanitarian Use Devices and FDA website for HDE indications*
- Cluster headache/headaches
- Tourette Syndrome
- Tardive Dyskinesia
- Multiple sclerosis (MS)
- Appetite disorders: anorexia nervosa/eating disorders and refractory obesity
- Epilepsy except as indicated above
- Head or voice tremor
- Huntington's disease
- Traumatic brain injury (TBI)
- Drug addiction
- Impulsive or violent behavior

**Policy Guidelines**

**Definitions**

**United Parkinson Disease Rating Scale (UPDRS):** UPDRS is a universal scale of Parkinson's disease (PD) symptoms, and it was created to comprehensively assess and document the exam of the patient with PD and be able to compare it with patient's future follow up visits, or to communicate about the progression of the PD symptoms in each patient with other neurologists.

The UPDRS is made up of the 1) Mentation, Behavior, and Mood, 2) ADL and 3) Motor sections. These are evaluated by interview. Some sections require multiple grades assigned to each extremity. A total of 199 points are possible. 199 represents the worst (total) disability), 0 no disability.

**Essential Tremor:** Uncontrolled shaking or trembling, usually of one or both hands or arms, that worsens when basic movements are attempted. It is caused by abnormalities in areas of the brain that control movement and is not tied to an underlying disease (e.g. Parkinson disease).

**Dystonia**: Highly variable neurological movement disorder characterized by involuntary muscle contractions. Dystonia results from abnormal functioning of the basal ganglia, a deep part of the brain which helps control coordination of movement. These regions of the brain control the speed and fluidity of movement and prevent unwanted movements. Patients with dystonia may experience uncontrollable twisting, repetitive movements, or abnormal postures and positions. These can affect any part of the body, including the arms, legs, trunk, face and vocal cords. Dystonia can affect young children to older adults of all races and ethnicities.

**Primary (Idiopathic) Dystonia**: Dystonia is the only sign, and secondary causes have been ruled out. Most primary dystonia's are variable, have adult onset, and are focal or segmental in nature. However, there are specific primary dystonia's with childhood or adolescent onset that have been linked to genetic mutations.

- Focal Dystonia: Is limited to one area of the body.
- Segmental Dystonia: Affects two or more parts of the body that are adjacent or close to one another.

**Parkinson's Disease**:

- **Idiopathic Parkinson's Disease**: Most common form of Parkinson's disease, and the cause essentially remains unknown. Parkinson's disease is a progressive disorder that is caused by a degeneration of nerve cells in the part of the brain called the substantia nigra, which controls movement. These nerve cells die or become impaired, losing the ability to produce an important chemical called dopamine.
- **Secondary Parkinsonism**: This is a disorder with symptoms similar to Parkinson's, but is caused by medication side effects, different neurodegenerative disorders, Illness, or brain damage.

**Seizures**

There are two broad categories of seizures: focal and generalized

Focal seizures (previously referred to as partial seizures) involve only one area of the brain, typically part of one lobe of one hemisphere. A focal (partial) seizure can be associated with impairment of consciousness or awareness (previously called complex partial seizure) or no impairment of consciousness (previously called simple partial seizures).

- Focal seizures without loss of consciousness: Once called simple partial seizures, these seizures do not cause loss of consciousness. They may alter emotions or change the way things look, smell, feel, taste or sound. They may also result in involuntary jerking of a body part, such as an arm or leg, and spontaneous sensory symptoms such as tingling, dizziness, and flashing lights.
- Focal seizures with impaired awareness: Once called complex partial seizures, these seizures involve a change or loss of consciousness or awareness. During a complex partial seizure, an individual may stare into space and not respond normally to their environment or perform repetitive movements, such as hand rubbing, chewing, swallowing, or walking in circles.

Generalized seizures: affect both cerebral hemispheres (sides of the brain) from the beginning of the seizure. They produce loss of consciousness, either briefly or for a longer period of time, and are sub-categorized into several major types:

- Generalized tonic clonic seizures (grand mal seizures)
- Myoclonic seizures
- Atonic seizures
- Absence seizures (petit mal)

# PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 61863 Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalmic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; first array
- 61864 each additional array
- 61867 Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalmic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; first array
- 61868 each additional array
- 61885 Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
- 61886 With connection to 2 or more electrode arrays
- C1767 Generator neurostimulator (implantable) non-rechargeable
- C1778 Lead, neurostimulator
- C1787 Patient programmer, neurostimulator
- C1816 Receiver and/or transmitter neurostimulator (implantable)
- C1820 Generator neurostimulator (implantable), non-high-frequency with rechargeable battery and charging system
- C1822 Generator neurostimulator (implantable) high frequency, with rechargeable battery and charging system
- C1897 Lead neurostimulator test kit (implantable)
- L8679 Implantable neurostimulator, pulse generator any type
- L8680 Implantable neurostimulator electrode, each
- L8681 Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only
- L8682 Implantable neurostimulator radiofrequency receiver
- L8683 Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver

- L8685 Implantable neurostimulator pulse generator, single array, rechargeable includes extension
- L8686 Implantable neurostimulator pulse generator, single array, nonrechargeable, includes extension
- L8687 Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
- L8688 Implantable neurostimulator pulse generator, dual array, nonrechargeable, includes extension
- L8689 External recharging system for battery (internal)for use with implantable neurostimulator, replacement only
- 95970 Electronic analysis of implanted neurostimulator pulse generator/transmitter (.e.g., contact group(s), interleaving, amplitude, pulse width, frequency [Hz], on/off cycle, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve neurostimulator pulse generator/transmitter without programming
- 95983 Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group(s), interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain neurostimulator pulse generator/transmitter programming, first 15 minutes face-to-face time with physician or other qualified health care professional
- 95984 Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group(s), interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain neurostimulator pulse generator/transmitter programming, each additional 15 minutes face-to-face time with physician or other qualified health care professional (List separately in addition to code for primary procedure)

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- UpToDate. Surgical treatment of essential tremor. Kelvin L. Chou M.D., Daniel Tarsy M.D., Topic last updated December 21, 2021. Also available at https://www.uptodate.com

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- UpToDate. Bipolar disorder in adults: overview of neuromodulation procedures. Paul Holtzheimer M.D., Topic last updated April 12, 2022. Also available at https://www.uptodate.com
- UpToDate. Tardive dyskinesia: prevention, treatment and prognosis. Tsao-Wei Liang M.D., Daniel Tarsy M.D. Topic last updated June 16, 2021. Also available at https://www.uptodate.com


# POLICY HISTORY

| Date | Reason | Action |
|---|---|---|
| July 2022 | Annual Review | Policy Renewed |
| July 2021 | Annual Review | Policy Renewed |
| July 2020 | Annual Review | Policy Revised |
| July 2019 | Annual Review | Policy Revised |
| August 2018 | Annual Review | Policy Revised |
| August 2017 | Annual Review | Policy Revised |
| August 2016 | Annual Review | Policy Revised |
| September 2015 | Annual Review | Policy Revised |
| February 2015 | Annual Review | Policy Revised |
| October 2014 | Annual Review | Policy Revised |
| January 2014 | Annual Review | Revised and New Policy Created |
| January 2013 | Annual Review | Policy Renewed |
| January 2012 | Annual Review | Policy Renewed |
| February 2011 | Interim Review | Policy Revised |
| October 2010 | Annual Review | Policy Renewed |

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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