Policy Statement

Unilateral deep brain stimulation of the thalamus may be considered medically necessary in patients with disabling, medically unresponsive tremor due to essential tremor or Parkinson disease.

Bilateral deep brain stimulation of the thalamus may be considered medically necessary in patients with disabling, medically unresponsive tremor in both upper limbs due to essential tremor or Parkinson disease.

Unilateral or bilateral deep brain stimulation of the globus pallidus or subthalamic nucleus may be considered medically necessary in patients with either of the following diagnoses and associated criteria:

- Parkinson disease and all of the following criteria are met:
  - A good response to levodopa
  - Motor complications not controlled by pharmacologic therapy
  - One of the following:
    - A minimum score of 30 points on the motor portion of the Unified Parkinson Disease Rating Scale when the patient has been without medication for approximately 12 hours
    - Parkinson disease for at least 4 years
- Patients are seven years of age or older with chronic, intractable (drug-refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis)

Deep brain stimulation is considered investigational for the treatment of other movement disorders, psychiatric, or neurologic disorders including, but not limited to:

- Alcohol addiction
- Alzheimer disease
- Anorexia nervosa
- Chronic cluster headaches
- Chronic pain
- Depression
- Epilepsy
- Multiple sclerosis
- Obsessive-compulsive disorder
- Post-traumatic dyskinesia
- Tardive dyskinesia
- Tourette syndrome

Policy Guidelines

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

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

Contraindications to deep brain stimulation include:

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

**Coding**
Coding for deep brain stimulation consists of a series of CPT codes describing the various steps of the procedure; i.e., implantation of the electrodes, implantation of the pulse generator, intraoperative monitoring and programming of the electrodes, and postoperative neuroprogramming. The following CPT codes are applicable.

**Implantation of Electrodes**
- 61850: Twist drill or burr hole(s) for implantation of neurostimulator electrodes, cortical
- 61863*: Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; first array
- 61864*: Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; each additional array (List separately in addition to primary procedure)
- 61867*: Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; first array
- 61868*: Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; each additional array (List separately in addition to primary procedure)

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

**Implantation of Pulse Generator**
- 61885: Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
- 61886: Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to 2 or more electrode arrays

**Electronic Analysis**
*Effective January 1, 2019, CPT codes 95983 and 95984 will replace CPT codes 95978 and 95979*
- 95970: 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, 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, cranial nerve, spinal cord, peripheral nerve, or sacral nerve, neurostimulator pulse generator/transmitter, with programming
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)

Neurostimulator analysis and programming is classified as either simple or complex. CPT codes
95983 and 95984 are time-based. Simple neurostimulators are defined as those affecting 3 or
fewer neurostimulatory parameters (e.g., pulse amplitude, duration, frequency, number of
electrode contacts) while a complex device affects more than 3 parameters. In the setting of
deep brain stimulation for tremor control, it is anticipated that the neuroprogramming and
analysis would be classified as simple. However, deep brain stimulation of the globus pallidus
and subthalamic nucleus stimulation requires intraoperative monitoring of more than 1 clinical
feature (i.e., rigidity, dyskinesia, and tremor) and the neuroprogramming would probably be
classified as complex.

Over time, patients may undergo several sessions of electronic analysis and programming to find
the optimal programming parameters. CPT codes 95970, 95983, and 95984, described here, may
be used.

The following HCPCS codes are for Deep Brain Stimulation:

- **L8680**: Implantable neurostimulator electrode, each
- **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

**Description**

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

**Related Policies**

- Responsive Neurostimulation for the Treatment of Refractory Focal Epilepsy
- Vagus Nerve Stimulation

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To
the extent there are any conflicts between these guidelines and the contract language, the
contract language will control. Please refer to the member's contract benefits in effect at the
time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

### Regulatory Status

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

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

In 2009, the Reclaim® device (Medtronic), a DBS device, was cleared for marketing by the FDA through the humanitarian device exemption process for the treatment of severe obsessive-compulsive disorder.

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

In 2016, the St. Jude Medical’s Infinity DBS device with directional leads was approved by the 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 2017, a second system with directional leads, the Vercise Deep Brain Stimulation System (Boston Scientific), was approved by the 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 antiepileptic medications.

FDA product code: MHY.
Rationale

Background
Deep Brain Stimulation
DBS involves the stereotactic placement of an electrode into the brain (i.e., hypothalamus, thalamus, globus pallidus, or subthalamic nucleus). The electrode is initially attached to a temporary transcutaneous cable for short-term stimulation to validate treatment effectiveness. Several days later, the patient returns for permanent subcutaneous surgical implantation of the cable and a radiofrequency-coupled or battery-powered programmable stimulator. The electrode is typically implanted unilaterally on the side corresponding to the most severe symptoms. However, use of bilateral stimulation using two electrode arrays has also been investigated in patients with bilateral, severe symptoms. After implantation, noninvasive programming of the neurostimulator can be adjusted to the patient’s symptoms. This feature may be important for patients with Parkinson disease (PD), whose disease may progress over time, requiring different neurostimulation parameters. Setting the optimal neurostimulation parameters may involve the balance between optimal symptom control and appearance of adverse effects of neurostimulation, such as dysarthria, disequilibrium, or involuntary movements.

Literature Review
Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function— including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Essential Tremor and Tremor in Parkinson Disease
Clinical Context and Therapy Purpose
Deep brain stimulation (DBS) has been investigated as an alternative to permanent neuroablative procedures, such as thalamotomy and pallidotomy. DBS has been most thoroughly investigated as an alternative to thalamotomy for unilateral control of essential tremor (ET) and tremor associated with PD. More recently, there has been research interest in the use of DBS of the globus pallidus or subthalamic nucleus as a treatment of other Parkinsonian symptoms, such as rigidity, bradykinesia, and akinesia. Another common morbidity associated with PD is the occurrence of motor fluctuations, referred to as “on and off” phenomena, related to the maximum effectiveness of drugs (i.e., “on” state) and the nadir response during drug troughs (i.e., “off” state). In addition, levodopa, the most commonly used anti-Parkinson drug, may be associated with disabling drug-induced dyskinesias. Therefore, the optimal pharmacologic treatment of PD may involve a balance between optimal effects on PD symptoms and the appearance of drug-induced dyskinesias. The effect of DBS on both PD symptoms and drug-induced dyskinesias has also been studied.
The question addressed in this evidence review is: does DBS improve the net health outcome in patients with ET or PD?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population(s) of interest are patients with ET or symptoms associated with PD.

**Interventions**
The therapy being considered is DBS, unilateral or bilateral stimulation of the thalamus as well as stimulation of the internal segment of the globus pallidus interna and subthalamic nucleus.

**Comparators**
PD is 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**
Key efficacy outcomes include motor scores, mobility, disability, activities of daily living and QOL quality of life. Key safety outcomes include death, stroke, depression, cognition infection and other device and procedure related events.

### Unilateral Stimulation of the Thalamus

This section was informed by a Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessment (1997) that focused on unilateral DBS of the thalamus as a treatment of tremor. The Assessment concluded:

- Tremor suppression was total or clinically significant in 82% to 91% of operated sides in 179 patients who underwent implantation of thalamic stimulation devices. Results were durable for up to eight years, and adverse events of stimulation were reported as mild and largely reversible.
- These results were at least as good as those associated with thalamotomy. An additional benefit of DBS is that recurrence of tremor may be managed by changes in stimulation parameters.

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

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

### Bilateral Stimulation of the Thalamus

Putzke et al (2005) reported on a series of 25 patients with ET treated with bilateral DBS for management of midline tremor (head, voice, tongue, trunk). Three patients died of unrelated causes, one patient was lost to follow-up due to transfer of care, and one patient did not have...
baseline evaluation; these patients were not included in the analysis. Patients were evaluated at baseline (before implantation of second stimulator), and at 1, 3, 6, 12, 24, and 36 months. At 12 months, evaluations were obtained from 76% of patients; at 36 months, 50% of patients were evaluated. The most consistent improvement on the Tremor Rating Scale during both unilateral and bilateral stimulation was found for head and voice tremor. The incremental improvement over unilateral stimulation through the first 12 months of bilateral stimulation was significant (p<0.01). For bilateral stimulation at months 3 and 12, outcome measures were significantly better than unilateral stimulation at month 3 (p<0.05). Small sample size limited analysis at months 24 and 36. Dysarthria was reported in 6 (27%) patients and disequilibrium in 5 (22%) patients after bilateral stimulation in staged implantations. No patient reported dysarthria and two reported disequilibrium before bilateral stimulation.

Pahwa et al (2006) reported on long-term follow-up of 45 patients who underwent thalamic DBS, 26 of whom had ET; of these patients, 18 had unilateral and 8 had bilateral implantation. Sixteen patients with unilateral and seven with bilateral stimulators completed at least part of the five-year follow-up evaluations. Patients with bilateral stimulation had a 78% improvement in mean motor tremor scores in the stimulation on state compared with baseline at 5-year follow-up (p=0.02) and 36% improvement in activities of daily living (ADL) scores. Patients with unilateral stimulation improved by 46% on motor tremor scores and 51% on ADL scores (p<0.01). Stimulation-related adverse events were reported in more than 10% of patients with unilateral and bilateral thalamic stimulators. Most were mild and were reduced with changes in stimulation parameters. Adverse events in patients with bilateral stimulation (e.g., dysarthria and other speech difficulties, disequilibrium or balance difficulties, abnormal gait) persisted, despite optimization of the stimulation parameters.

**Directional Deep Brain Stimulation**

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

**Section Summary: Essential Tremor and Tremor in Parkinson Disease**

A TEC Assessment concluded there was sufficient evidence that DBS of the thalamus results in clinically significant tremor suppression and that outcomes after DBS were at least as good as thalamotomy. Subsequent studies reporting long-term follow-up have supported the conclusions of the TEC Assessment and found that tremors were effectively controlled five to six years after DBS. A new technology in DBS systems, using directional leads, has recently emerged and data evaluating the new technology is expected to be published in 2018.

**Symptoms Associated with Parkinson Disease**

**Advanced Parkinson Disease**

**Stimulation of the Internal Segment of the Globus Pallidus Interna and Subthalamic Nucleus**

This section was informed by a TEC Assessment (2001) that focused on the use of DBS of the internal segment of the globus pallidus interna (GPi) and subthalamic nucleus (STN) for a broader range of PD symptoms. The Assessment concluded:

- A wide variety of studies have consistently demonstrated that DBS of the GPi or STN results in significant improvements, as measured by standardized rating scales of neurologic function. The most frequently observed improvements consist of increased waking hours spent in a state of mobility without dyskinesia, improved motor function during “off” periods when levodopa is not effective, reduction in frequency and severity of levodopa-induced dyskinesia during periods when levodopa is working (“on” periods),
Deep Brain Stimulation

improvement in cardinal symptoms of PD during periods when medication is not working, and in the case of bilateral DBS of the STN, reduction in the required daily dosage of levodopa and/or its equivalents. The magnitude of these changes were both statistically significant and clinically meaningful.

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

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

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

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

Parkinson Disease with Early Motor Complications

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

The primary endpoint was mean change from baseline to 2 years in the summary index of the Parkinson Disease Questionnaire, which has a maximum score of 39 points, with higher scores indicating higher QOL. Mean baseline scores on the Parkinson Disease Questionnaire were 30.2 in the DBS plus medical therapy group and 30.2 in the medical therapy only group. At two 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 three 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.

**GPI vs STN Stimulation**

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

**Section Summary: Symptoms Associated with Parkinson Disease**

A number of RCTs and systematic reviews of the literature have been published. A TEC Assessment concluded that studies 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. One RCT compared DBS plus medical therapy with medical therapy alone in patients with levodopa-responsive PD of at least four years in duration and uncontrolled motor symptoms. The trial found that QOL at two years (e.g., motor disability, motor complications) was significantly higher when DBS was added to medical therapy. Meta-analyses of RCTs comparing GPI and STN have had inconsistent findings and did not conclude that one type of stimulation was clearly superior to the other.

**Dystonia**

**Clinical Context and Therapy Purpose**

DBS has also been investigated in patients with primary and secondary dystonia, defined as a neurologic movement disorder characterized by involuntary muscle contractions, which force certain parts of the body into abnormal, contorted, and painful movements or postures. Dystonia can be classified according to age of onset, bodily distribution of symptoms, and cause. Age of onset can occur during childhood or during adulthood. Dystonia can affect certain portions of the body (focal dystonia and multifocal dystonia) or the entire body (generalized dystonia). Torticollis is an example of a focal dystonia.

DBS for the treatment of primary dystonia received the 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 ten 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.

The question addressed in this evidence review is: does DBS improve the net health outcome in patients with primary or secondary dystonia?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population(s) of interest are patients 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.

**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**
Key efficacy outcomes include clinical severity of dystonia and disability as rated using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) or Toronto Western Spasmodic Torticollis Rating scale (TWSTRS) and QOL.

The 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 patient’s 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.

TWSTRS is most commonly 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.

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

**Primary Dystonia**

**Systematic Reviews**
Moro et al (2017) published a systematic review of literature published through November 2015 on primary dystonia (also known as isolated dystonia). Reviewers included studies with at least ten cases. Fifty-eight articles corresponding to 54 unique studies were identified; most involved bilateral DBS of the GPi. There were only 3 controlled studies, 2 RCTs (Kupsch et al 2006 and Volkmann et al 2014; described below) and 1 study that included a double-blind
evaluation with and without stimulation. Rodrigues et al (2019) performed a Cochrane systematic review of RCTs and identified the same 2 RCTs.23.

**Randomized Controlled Trials**

The two RCTs identified in the systematic reviews are described in Tables 1-4. Kupsch et al (2006) randomized 40 patients with primary segmental or generalized dystonia to DBS or sham stimulation for 3 months.24 The primary outcome was change from baseline to three months in the severity of symptoms measured by the BFMDRS assessed by blinded reviewers from videotaped sessions. All patients subsequently received open-label DBS for six months after blinded treatment. Results are shown in Table 2. In brief, the change from baseline in the mean BFMDRS movement score was significantly greater in the DBS group.

The Volkmann et al (2014) RCT was patient- and observer-blinded evaluation of pallidal neurostimulation in subjects with refractory cervical dystonia.25 The trial included 62 adults with cervical dystonia for 3 or more years in duration, a severity score of 15 or more on the 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 (three months); thereafter, all patients received open-label active stimulation. Results are shown in Table 2. 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). 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, seven patients experienced dysarthria (i.e., slightly slurred speech), which was not reversible in six patients.

**Table 1. Characteristics of RCTs of DBS for Primary Dystonia**

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kupsch (2006); NCT00142259</td>
<td>Germany, Norway, Austria</td>
<td>10</td>
<td>2002 to 2004</td>
<td>Patients ages 14 to 75 years with marked disability owing to primary generalized or segmental dystonia despite optimal pharmacologic treatment with disease duration of at least 5 years</td>
<td>N=20</td>
</tr>
<tr>
<td>Volkmann (2014); NCT00148889</td>
<td>Germany, Norway, Austria</td>
<td>10</td>
<td>2006 to 2008</td>
<td>Adults under age of 75 with idiopathic or inherited isolated cervical dystonia with disease duration 3 years or longer and ≥15 on the TWSTRS</td>
<td>N=32</td>
</tr>
</tbody>
</table>

GPi: globus pallidus internus; TWSTRS: Toronto Western Spasmodic Torticollis Rating Scale; RCT: randomized controlled trial; DBS: deep brain stimulation.
### Table 2. Results of RCTs of DBS for Primary Dystonia

<table>
<thead>
<tr>
<th>Study</th>
<th>Dystonia severity</th>
<th>Disability</th>
<th>Quality of life</th>
<th>Depression symptoms</th>
<th>Serious Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kupsch (2006)</td>
<td>Change in BFMDRS movement at 3 months, Mean (SD)</td>
<td>39 (2.9)</td>
<td>10.1 (7.4)</td>
<td>-5.1 (8.4)</td>
<td>3 (8%) related to lead dislodgement or 1 related to infection requiring hospitalization</td>
</tr>
<tr>
<td>N</td>
<td>40</td>
<td>33</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBS</td>
<td>-15.8 (14.1)</td>
<td>3.9 (2.9)</td>
<td>PCS: 10.1 (7.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham</td>
<td>-1.4 (3.8)</td>
<td>0.8 (1.2)</td>
<td>PCS: 3.8 (8.4)</td>
<td>-0.5 (10.2)</td>
<td></td>
</tr>
</tbody>
</table>

**Treatment effect**
- MD = 14.40 (8.0 to 20.80); p < 0.01
- MD = 3.10 (1.72 to 4.48)
- PCS MD = 6.30 (1.06 to 11.54)
- MCS MD = 5.00 (-2.14 to 12.14)
- MD = 4.60 (-2.06 to 11.26)

**BFMDRS:** Burke-Fahn-Marsden-Dystonia-Rating-Scale; **TWSTRS:** Toronto Western Spasmodic Torticollis Rating Scale; **MD:** Mean difference; **BDI:** Beck Depression Inventory; **SF-36:** short form 36 item quality of life survey, PCS: Physical Component Score; MCS: Mental component score; **CI:** confidence interval; **DBS:** deep brain stimulation; **RCT:** randomized controlled trial; **SD:** standard deviation.

### Table 3. Relevance Limitations: RCTs of DBS for Primary Dystonia

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kupsch (2006)</td>
<td>1: Only 3 months of double-blind study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volkmann (2014)</td>
<td>1: Only 3 months of double-blind study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**RCT:** randomized controlled trial; **DBS:** deep brain stimulation.

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

- Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
- Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
- Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
#### Table 4. Study Design and Conduct Limitations: RCTs of DBS for Primary Dystonia

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation</th>
<th>Blinding</th>
<th>Selective Reporting</th>
<th>Data Completeness</th>
<th>Power</th>
<th>Statistical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kupsch (2006)</td>
<td>1: Registered after enrollment was complete</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volkmann (2014)</td>
<td>1,3: Treating physicians not blinded. Primary outcome assessors blinded but secondary outcomes subject to bias</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**RCT**: randomized controlled trial; **DBS**: deep brain stimulation.

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

- **Blinding key**: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
- **Selective Reporting key**: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
- **Data Completeness key**: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
- **Power key**: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
- **Statistical key**: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

### Section Summary: Primary Dystonia

A review prepared for the FDA and systematic reviews have evaluated evidence on DBS for primary dystonia. There are numerous small case series and two RCTs. Both RCTs found that severity scores improved more after active than after sham stimulation. A pooled analysis of 24 studies, mainly uncontrolled, found improvements in motor scores and disability scores after 6 months and at last follow-up (mean, 32 months).

### Tardive Dyskinesia and Tardive Dystonia

#### Randomized Controlled Trials

One RCT has been conducted of pallidal DBS in patients with tardive dystonia. Characteristics are shown in Table 5 and results are in Table 6. Briefly, Gruber et al (2018) assessed dystonia/dyskinesia severity using the BFMDRS at 3 months between active vs sham DBS. Twenty-five patients were randomized. In the intention-to-treat analyses, the between group difference of dystonia severity was not significant at three months. Adverse events occurred in 10/25 of patients; 3 of the adverse events were serious. The study was originally powered to include 48 patients but only 25 were randomized and analyses may be underpowered.

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Active</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gruber 2018; NCT00331669</td>
<td>Germany</td>
<td>15</td>
<td>2006 to 2009</td>
<td>Adults with tardive dystonia disease duration of at least 18 months with marked disability and deterioration of activities of daily living owing to tardive dystonia despite medical treatment</td>
<td>N=12</td>
<td>N=13</td>
</tr>
</tbody>
</table>

**RCT**: randomized controlled trial; **DBS**: deep brain stimulation.
### Table 6. Results of RCTs of DBS for Tardive Dyskinesia and Tardive Dystonia

<table>
<thead>
<tr>
<th>Study</th>
<th>Dystonia severity</th>
<th>Disability</th>
<th>Quality of life</th>
<th>Depression symptoms</th>
<th>Serious Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gruber 2018</td>
<td>Change in BFMDRS</td>
<td>Change in BFMDRS Disability score</td>
<td>Change in SF-36 at 3 mon, Mean (SD)</td>
<td>HAM-D at 3 mon, Mean (SD)</td>
<td>3 events (episodes of confusion, worsening of dystonia following gastrointestinal infection, skin erosion)</td>
</tr>
</tbody>
</table>

- Gruber 2018: Change in BFMDRS Movement score at 3 mon, Mean (SD): -5.6 (9.1); Change in BFMDRS Disability score at 3 mon, Mean (SD): -5.9 (13.9).
- DBS: -5.6 (9.1) vs. Sham -5.9 (13.9).
- Sham: -5.9 (13.9) vs. DBS -5.6 (9.1).
- Treatment effect (95% CI): p=0.72

BFMDRS: Burke-Fahn-Marsden-Dystonia-Rating-Scale; HAM-D: Hamilton Depression Score; SF-36: short form 36 item quality of life survey, PCS: Physical Component Score; MCS: Mental Component Score; DBS: deep brain stimulation; RCT: randomized controlled trial; SD: standard deviation.

### Table 7. Relevance Limitations: RCTs of DBS for Tardive Dyskinesia and Tardive Dystonia

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gruber 2018</td>
<td>1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.</td>
<td>1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.</td>
<td>1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.</td>
<td>1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.</td>
<td>1. 3 mon follow-up in blinded period</td>
</tr>
</tbody>
</table>

DBS: deep brain stimulation; RCT: randomized controlled trial.

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

### Table 8. Study Design and Conduct Limitations: RCTs of DBS for Tardive Dyskinesia and Tardive Dystonia

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation</th>
<th>Blinding</th>
<th>Selective Reporting</th>
<th>Data Completeness</th>
<th>Power</th>
<th>Statistical</th>
</tr>
</thead>
</table>
Case series

Stimulation of the GPi was examined as a treatment for tardive dyskinesia in a multicenter case series by Damier et al (2007), with a double-blind evaluation at 6 months (comparison of symptoms in the on and off positions).27 The trial was stopped early due to successful treatment (>40% improvement at 6 months) in the first 10 patients. In the double-blind evaluation of these patients, stimulation was associated with a mean decrease of 50% in the symptom score when the device was on vs off.

Outcomes on motor function, QOL, and mood in a series of 9 patients treated with DBS of the GPi for tardive dystonia were reported by Grueter et al (2009).28 One week, and 3 to 6 months after surgery, BFMDRS motor scores were improved by 56.4% and 74.1%, BFMDRS disability scores by 62.5% and 88.9%, and Abnormal Involuntary Movement Scale scores by 52.3% and 69.5%, respectively. At last follow-up (mean, 41 months; range, 18-90 months), BFMDRS motor scores were reduced compared with presurgical assessment by 83%, BFMDRS disability score by 67.7%, and Abnormal Involuntary Movement Scale scores by 78.7%.

Pouclet-Courtemanche et al (2016) reported on a case series of 19 patients with severe pharma-co-resistant tardive dyskinesia treated with DBS.29 Patients were assessed after 3, 6, and 12 months after the procedure. At 6 months, all patients had experienced greater than 40% reduction in symptoms as measured on the Extrapyramidal Symptoms Rating Scale. At 12 months, the mean decrease in Extrapyramidal Symptoms Rating Scale score was 58% (range, 21%-81%).

Section Summary: Tardive Dyskinesia and Tardive Dystonia

Evidence for the use of DBS to treat tardive syndromes consists of an RCT with three months of blinded follow-up and case series with follow-up of six months to approximately four years. The RCT did not report statistically significant improvement in the dystonia severity outcomes or the secondary outcomes related to disability and QOL for DBS compared to sham but the study did not recruit the number of patients for which it was originally powered. Case series reported favorable results with DBS treatment.

Epilepsy

Clinical Context and Therapy Purpose

Approximately one-third of patients with epilepsy do not respond to anti-epileptic drugs and are considered to have drug-resistant epilepsy. Patients with drug-resistant or refractory epilepsy have a higher risk of death as well as a high burden of epilepsy-related disabilities and limitations.

The question addressed in this evidence review is: does DBS improve the net health outcome in patients with epilepsy?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population(s) of interest are patients with epilepsy refractory to medical treatment who are not candidates for resective surgery. The International League Against Epilepsy defined drug-resistant as failure of adequate trials of two tolerated, appropriately chosen and administered anti-epileptic drugs, used as monotherapy or in combination, to achieve seizure freedom.30 Patients who are not candidates for resective surgery include those multifocal seizure onset, significant medical comorbidities or generalized-onset epilepsy.
Interventions
The therapy being considered is DBS. Several areas of the brain have been targeted.

Comparators
The treatment for chronic epilepsy consists of anti-epileptic drugs. A ketogenic diet may be used as an adjunctive treatment. For patients with epilepsy that is refractory to medical treatment, surgery options such as resection or disconnection may be considered.

Vagus nerve stimulation may also be used in patients with drug-refractory epilepsy who are not candidates for resective surgery.

Sham control may be used in RCTs.

Outcomes
Key efficacy outcomes include measures 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 QOL. The Quality of Live Inventory in Epilepsy (QOLIE-31) is a tool used to assess the impact of antiepileptic treatment on patients' lives; the minimally important change in patients with treatment-resistant seizures was 5 points.

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

Study Selection Criteria
1. To assess efficacy outcomes, comparative controlled prospective trials were included, with a preference for RCTs.
2. In the absence of such trials, comparative observational studies, with a preference for prospective studies will be included.
3. To assess long-term outcomes and adverse effects, single arm studies that captured longer periods of follow-up and/or larger populations may be included.
4. Studies with duplicative or overlapping populations will be excluded.

Systematic Reviews
A Cochrane systematic review on deep brain and cortical stimulation for epilepsy was published in 2017 and included RCTs published through 2016. The review included 1 trial on anterior thalamic nucleus DBS for multifocal epilepsy (n=109, see discussion in following section), 1 trial on centromedian thalamic DBS for multifocal or generalized epilepsy (n=7), and 3 RCTs on hippocampal DBS for medial temporal lobe epilepsy (n=15). Meta-analyses provided estimates by site of stimulation. The RCT using anterior thalamic nucleus DBS will be discussed in the following section.

Two systematic reviews on the use of DBS for drug-resistant epilepsy, both published in 2018, assessed many of the same studies. The larger review, by Li et al (2018), identified 10 RCTs and 48 uncontrolled studies. The literature search date was not reported. Meta-analyses were not performed. The largest RCT in which DBS targeted the anterior nucleus of the thalamus Fisher et al (2010) is described below. Reviewers concluded that more robust clinical trials would be needed.

Randomized Controlled Trials
Trials including 15 patients or more will be described in more detail in this section. Study characteristics are in Table 9 and results are in Table 10. Tables 11 and 12 describe study limitations.

Fisher et al (2010) conducted a U.S. multicenter, double-blind, randomized trial, Stimulation of the Anterior Nuclei of the Thalamus for Epilepsy (SANTE) (see Table 1). Included were 110 patients, ages 18 to 65 years, who experienced at least 6 partial seizures (including secondarily...
generalized seizures) per month, but no more than 10 per day. (An additional 47 patients were enrolled in the trial but did not undergo implantation.) At least three antiepileptic drugs must have failed to produce adequate seizure control before baseline, with one to four antiepileptic drugs used at the time of study entry. Patients were asked to keep a daily seizure diary during treatment. All patients received DBS device implantation, with half the patients randomized to stimulation (n=54) and half to no stimulation (n=55) during a 3-month blinded phase; thereafter all patients received unblinded stimulation. Baseline monthly median seizure frequency was 19.5. During the first and second months of the blinded phase, the difference in seizure reduction between stimulation on (-42.1%) and stimulation off (-28.7%) did not differ significantly. In the last month of the blinded phase, the stimulated group had a significantly greater reduction in seizures (-40.4%) than the control group (-14.5%; p=0.002; see Table 10). The publication stated that changes in additional outcome measures did not show significant treatment group differences during the double-blind phase, including 50% responder rates, Liverpool Seizure Severity Scale (LSSS), QOLIE-31 scores but data were not shown. Data for these outcomes are available in the FDA Summary of Safety and Effectiveness (SSED), see Table 10.36

Troster et al (2017) assessed neuropsychological adverse events from the SANTE trial during the 3-month blinded phase, and at 7-year follow-up during the open-label noncomparative phase (see Table 9).37 At baseline, there were no differences in depression history between groups. During the 3-month blinded phase of the trial, depression was reported in 8 (15%) patients from the stimulation group and in 1 (2%) patient from the no stimulation group (p=0.02). At the seven-year follow-up, after the treatment groups had been combined, there was no statistically significant difference in Profile of Mood State depression score compared with baseline. Memory adverse events also occurred at significantly different rates between the treatment groups during the blinded phase (seven in the active group, one in the control group; p=0.03). At the seven-year follow-up, most cognitive function tests did not improve over baseline measurements.

Cukiert et al (2017) conducted a double-blind, placebo-controlled randomized trial evaluating 16 patients with refractory temporal lobe epilepsy (see Table 9).38 All patients underwent DBS device implantation, and were followed for six months. Patients were seen weekly to receive the treatment or placebo. To maintain double-blind status, programming was performed by a nontreating assistant. Patients kept a seizure diary during the study period. Patients were considered seizure-free if no seizures occurred during the last two months of the trial. Responders were defined as patients experiencing a reduction of 50% or more in frequency reduction. Results are summarized in Table 9.

Table 9 Summary of RCT Characteristics for Epilepsy

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher et al (2010)35; Troster et al (2017)37; SANTE</td>
<td>U.S.</td>
<td>17</td>
<td>NR</td>
<td>Patients with partial seizures, including secondary generalized seizures, refractory to ≥3 medications</td>
<td>5-V stimulus intensity (n=54)</td>
</tr>
<tr>
<td>Cukiert et al (2017)38.</td>
<td>Brazil</td>
<td>1</td>
<td>2014-2016</td>
<td>Patients with temporal lobe epilepsy, refractory to ≥3 medications</td>
<td>Weekly 0.4-V to 2-V stimulus intensity (n=8)</td>
</tr>
</tbody>
</table>

NR: not reported; RCT: randomized controlled trial; V: volts.
Table 10. Summary of RCT Outcomes for Epilepsy

<table>
<thead>
<tr>
<th>Study</th>
<th>Seizure Reduction, % (p)</th>
<th>Responder (50% or more reduction in seizure frequency)</th>
<th>Hospitalizations Mean (SD) annual hospitalizations per patient</th>
<th>Rescue medication (at least one use)</th>
<th>Seizure severity</th>
<th>Quality of life</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td></td>
<td>1</td>
<td>2                  3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher et al (2010)35;</td>
<td></td>
<td>30%</td>
<td>0.08 (0.56)</td>
<td>22%</td>
<td>-8.2 (17.8)</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Troster et al (2017)37;</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>SANTE DBS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham</td>
<td></td>
<td>26%</td>
<td>0.37 (1.17)</td>
<td>22%</td>
<td>-6.8 (19.6)</td>
<td>2.8</td>
<td></td>
</tr>
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<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between-group difference</td>
<td>-11% (NS)</td>
<td>-11% (NS)</td>
<td>-29% (0.002)</td>
<td>p=0.83a</td>
<td>p=0.11a</td>
<td>p=0.87a</td>
<td>p=0.70a</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIAS at 6 Months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cukiert et al (2017)38</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stimulation on</td>
<td></td>
<td>4 seizure-free; 3 responders; 1 no response</td>
<td>2 patients with local skin erosions at cranial site of implant, treated with antibiotics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stimulation off</td>
<td></td>
<td>0 seizure-free; 3 responders; 5 no response</td>
<td>2 patients with local skin erosions at cranial site of implant, treated with antibiotics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FIAS: focal impaired awareness seizure; RCT: randomized controlled trial; NS: not statistically significant; SD: standard deviation; LSSS: Liverpool Seizure Severity Scale; QOLIE-31: Quality of Life in Epilepsy Score.
aNot reported in publication but reported in FDA SSED.

Study limitations are described in Tables 11 and 12. The SANTE study included relevant patients and outcomes and had few design and conduct limitations. Both RCTs were missing report of several important outcomes such as QOL and functional outcomes in the publications although SANTE outcomes are available in the FDA SSED. Cukiert et al (2017) did not include information on power/sample size, flow of participants and missing data.

Table 11. Relevance Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Populationa</th>
<th>Interventionb</th>
<th>Comparatorc</th>
<th>Outcomesd</th>
<th>Follow-Upce</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher et al (2010)35;</td>
<td></td>
<td></td>
<td></td>
<td>1: Responder and freedom from seizure, quality of life outcomes not reported in publication; reported in SSED.</td>
<td></td>
</tr>
<tr>
<td>SANTE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cukiert et al (2017)38</td>
<td></td>
<td></td>
<td></td>
<td>1: Quality of life and functional outcomes not reported</td>
<td></td>
</tr>
<tr>
<td>SSED: Summary of Safety and Effectiveness.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Table 12: Study Design and Conduct Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation</th>
<th>Blinding</th>
<th>Selective Reporting</th>
<th>Power</th>
<th>Statistical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher et al (2010)</td>
<td>2. Several seizure outcomes as well as quality of life collected but not reported in publication; available in SSED.</td>
<td>1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.</td>
<td>2. Not clear if analyses were done independently for each time point or if analyses adjusted for multiple observations; 4. Comparative treatment effects not calculated.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cukiert et al (2017)</td>
<td>2. No mention of how missing diary data or other missing data were handled in analysis. No flow of participants described.</td>
<td>1. No power calculations</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SSED: Summary of Safety and Effectiveness.

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

Observational Studies

Long-term outcomes of the SANTE trial were reported by Salanova et al (2015). The uncontrolled open-label portion of the trial began after 3 months and, beginning at 13 months, stimulation parameters could be adjusted at the clinician’s discretion. Of the 110 implanted patients, 105 (95%) completed the 13-month follow-up, 98 (89%) completed the 3-year follow-up, and 83 (75%) completed 5 years. Among patients with at least 70 days of diary entries, the
median change in seizure frequency from baseline was 41% at 1 year and 69% at 5 years (p<0.001 for both). During the trial, 39 (35%) of 110 patients had a device-related serious adverse event, most of which occurred in the first months after implantation. They included implant-site infection (10% of patients) and lead(s) not within target (8.2% of patients). Seven deaths occurred during the trial and none was considered to be device-related. Depression was reported in 41 (37%) patients following implant; in 3 cases, it was considered device-related. Memory impairment (nonserious) was reported in 30 (27%) patients during the trial, half of whom had a history of the condition.

A seven-year follow-up of SANTE was reported in the FDA SSED. Seventy-three (66% of implanted) patients completed the year 7 visit. Reasons for withdrawals from the study after implantation were: death (6), withdrawal of consent (5), investigator decision (3), therapeutic product ineffective (13), implant site infection or pain (6), other adverse event (7) and elective device removal (1). Fifty patients were included in the year 7 analysis of responder rate; see Table 13. Seventy-four percent of the 50 patients were responders (50% or greater reduction in seizure frequency). QOLIE-31 scores (n=67) improved by a mean of 4.9 (SD=11) points at year 7. LSSS scores (n=67) improved by a mean of 18 points (SD=23) at year 7. As the FDA documentation notes, interpretation of the long-term follow-up is limited by several factors: patients were aware they were receiving DBS, only 66% of implanted patients completed the year 7 visit and those who did not do well may be more likely to leave the study, and changes in anti-epileptic drugs were allowed in long-term follow-up.

**Table 13. 7-Year Outcomes from SANTE**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Median seizure frequency (change from BL)</th>
<th>Responders (≥50% reduction in seizure frequency)</th>
<th>LSSS, Mean (SD)</th>
<th>QOLIE-31, ≥5 point improvement</th>
<th>Hospitalizations, mean (SD) annual number of hospitalizations per patients</th>
<th>Serious device-related adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>50</td>
<td>50</td>
<td>67</td>
<td>67</td>
<td>80</td>
<td>110</td>
</tr>
<tr>
<td>Estimate</td>
<td>-75%</td>
<td>74%</td>
<td>-18.1 (23.5)</td>
<td>43%</td>
<td>0.08 (0.28)</td>
<td>34.5%</td>
</tr>
</tbody>
</table>

LSSS: Liverpool Seizure Severity Scale; QOLIE-31: Quality of Life in Epilepsy Score; SD: standard deviation; BL: baseline.

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

**Section Summary: Epilepsy**

A systematic review identified several RCTs and many observational studies in which DBS was evaluated for the treatment of epilepsy. Many different targets have been investigated and most of the RCTs included fewer than 15 patients. The largest RCT consisted of a three-month blinded phase in which patients were randomized to stimulation or no stimulation targeting the anterior nucleus of the thalamus. After the randomized phase, all patients received stimulation and were followed for 13 additional months. Findings in the first three months were mixed: patients reported significantly fewer seizures in the third month but not in the first or second month. There were no differences between groups in 50% responder rates, LSSS, or QOLIE-31 scores. In the uncontrolled follow-up period of the RCT and in many small observational studies, patients reported fewer seizures compared with baseline, however, without a control group, interpretation of results is limited. In addition interpretation of seven-year follow-up of SANTE is limited by high loss to follow-up. Serious adverse events were reported in about one-third of patients. The risk-benefit ratio is uncertain. DBS has not been directly compared to vagus.
nerve stimulation, another treatment used in patients with drug-refractory epilepsy who are not candidates for resective surgery.

**Tourette Syndrome**

**Clinical Context and Therapy Purpose**

Tourette Syndrome (TS) is a neurological disorder marked by multiple motor and phonic tics with onset during childhood or early adulthood and which often improve in adulthood. Children with TS frequently have other comorbid conditions such as attention deficit hyperactivity disorder or obsessive-compulsive disorder (OCD).

The question addressed in this evidence review is: does DBS improve the net health outcome in patients with TS?

The following PICOTS were used to select literature to inform this review.

**Patients**

The population of interest are patients with TS who have disabling tics that are refractory to optimal medical management.

**Interventions**

The therapy being considered is DBS. Several targets have been investigated such as the medial thalamus at the crosspoint of the centromedian nucleus, substantia periventricularis, and nucleus ventro-oralisintemus, STN, caudate nucleus, Gpi, and the anterior limb of the internal capsule and nucleus accumbens.

**Comparators**

Intervention may be initiated when symptoms of TS are disabling or causing difficulty in functioning. Patients may require a therapy to treat tics as well as comorbid attention deficit hyperactivity disorder or OCD. Medication treatment for tics might include antidopaminergic drugs, alpha adrenergic agonists drugs, topiramate or injections of botulinum toxin. Behavioral therapy, primarily based on habit reversal therapy is also used.

**Outcomes**

Key efficacy outcomes include measures of motor impairment, tic severity (Yale Global Tic Severity Scale [YGTSS]), functional ability and disability, medication use and QOL. The overall score for the YGTSS is on a scale from 0 to 100, with lower scores indicating less severe symptoms, it has a motor tic and verbal tick subscale.

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

**Study Selection Criteria**

1. To assess efficacy outcomes, comparative controlled prospective trials were included, with a preference for RCTs.
2. In the absence of such trials, comparative observational studies, with a preference for prospective studies will be included.
3. To assess long-term outcomes and adverse effects, single arm studies that captured longer periods of follow-up and/or larger populations may be included.
4. Studies with duplicative or overlapping populations will be excluded.

**Systematic Reviews**

Several systematic reviews of the literature on DBS for TS have been published. 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 DBS for TS, 4 of which were randomized crossover studies. The studies included a total of 156 cases. Twenty-four studies included a single patient and 4 had sample
sizes of 10 or more (maximum, 18 patients). Half of the patients (n=78) received thalamus stimulation and the next most common areas of stimulation were the Gpi anteromedial part (n=44) and post ventrolateral part (n=20). Two of the RCTs used thalamic stimulation, one used bilateral globus pallidus stimulation, and one used both. The primary outcome was the 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 (standard mean difference=0.96; 95% CI, 0.36 to 1.56). Reviewers noted that the effect size of 0.96 would be considered large.

**Randomized Controlled Trials**

Trials including 15 patients or more will be described in more detail in this section. Study characteristics are shown in Table 14 and results are shown in Table 15.

The crossover RCT was published by Kefalopoulou et al (2015).46 The double-blind trial included 15 patients with severe medic ally refractory Tourette syndrome; all received bilateral Gpi surgery for DBS and were randomized to the off-stimulation phase first or the on-stimulation phase first for 3 months, followed by the opposite phase for the next 3 months. Of the 15 receiving surgery, 14 were randomized and 13 completed assessments after both on and off phases. For the 13 trial completers, mean YGTSS scores were 80.7 in the off-stimulation phase and 68.3 in the on-stimulation phase. The mean difference in YGTSS scores indicated an improvement of 12.4 points (95% CI, 0.1 to 24.7 points), which was statistically significant (p=0.048) after Bonferroni correction. There was no significant between-group difference in YGTSS scores for patients randomized to the on-stimulation phase first or second. Three serious adverse events were reported, two related to surgery and one related to stimulation.

Welter et al (2017) reported results of a sham-controlled RCT of 3 months of anterior internal globus pallidus (aGpi) DBS in 17 adults with severe TS.47 The primary endpoint was difference in YGTSS score between the beginning and end of the three month double-blind period. The study was powered to detect a benefit amounting to a 30-point reduction in YGTSS score in the active DBS group and may, therefore, have been underpowered to detect smaller changes in YGTSS. There was no significant difference in YGTSS score change between groups (active DBS median change 1.1% [IQR –23.9 to 38.1] vs sham DBS median change 0.0% [-10.6 to 4.8]; p=0.39). There was also no difference between groups in change in co-morbid symptoms of OCD or depression or QOL. There were 15 serious adverse events in 13 patients: infections in 4 patients, 1 electrode misplacement, 1 episode of depressive signs, and 3 episodes of increased tic severity and anxiety.

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kefalopoulou et al (2015); NCT01647269</td>
<td>UK</td>
<td>2</td>
<td>2009 to 2013</td>
<td>Adults with TS with chronic and severe tic, with severe functional impairment (12+ months), had not responded to conventional medical treatment, behavioral intervention had been thought inappropriate or had been unsuccessful</td>
<td>Stimulation on (Bilateral globus pallidus internus [Gpi] DBS)</td>
</tr>
</tbody>
</table>
Table 15. Results of RCTs of DBS for Tourette Syndrome

<table>
<thead>
<tr>
<th>Study</th>
<th>Tic severity</th>
<th>Co-morbid symptoms</th>
<th>Quality of life</th>
<th>Depression symptoms</th>
<th>Serious Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kefalopoulou et al (2015)</td>
<td>YGTSS, Mean (SD) at 3 months</td>
<td>Y-BOCS, Mean (SD) at 3 months</td>
<td>GTSS-QOL, Mean (SD) at 3 months</td>
<td>Beck Depression Inventory, Mean (SD) at 3 months</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>15ª</td>
<td>15ª</td>
<td>15ª</td>
<td>15ª</td>
<td>15ª</td>
</tr>
<tr>
<td>DBS</td>
<td>68.3 (18.6)</td>
<td>12.8 (10.0)</td>
<td>54.3 (28.4)</td>
<td>21.0 (13.8)</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>No stimulation</td>
<td>80.7 (12.0)</td>
<td>14.6 (10.3)</td>
<td>62.0 (24.7)</td>
<td>20.5 (14.3)</td>
<td></td>
</tr>
<tr>
<td>Treatment effect (95% CI)</td>
<td>12.4 (0.1 to 24.7, p=0.05)</td>
<td>p=0.98</td>
<td>p=0.04</td>
<td>p=0.13</td>
<td></td>
</tr>
<tr>
<td>Welter et al (2017)</td>
<td>YGTSS, Mean change (CI) at 3 months</td>
<td>Y-BOCS, Mean change (CI) at 3 months</td>
<td>SF-36, Mean change (CI) at 3 months</td>
<td>MADRS, Mean change at 3 months</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>DBS</td>
<td>-4.5 (-12.5 to 0.5)</td>
<td>-3.5 (-6.8 to 0.3)</td>
<td>PCS6.1 (1.2 to 8.7):</td>
<td>-2.0 (-6.0 to 0.5)</td>
<td>15 serious adverse events (three in patients who withdrew before stimulation and six each in the active and sham stimulation groups) occurred in 13 patients: infections in four patients, one electrode misplacement, one episode of depressive signs, and three episodes of increased tic severity and anxiety</td>
</tr>
<tr>
<td>No stimulation</td>
<td>5.0 (-2.5 to 17.5)</td>
<td>0.0 (-1.0 to 0.0)</td>
<td>PCS-0.4 (-3.1 to 16.1):</td>
<td>0.0 (-2.3 to 1.8)</td>
<td></td>
</tr>
<tr>
<td>Treatment effect (95% CI)</td>
<td>p=0.39</td>
<td>p=0.25</td>
<td>PCSp&gt;0.99</td>
<td>MCSp=0.14</td>
<td>p=0.25</td>
</tr>
</tbody>
</table>

YGTSS: Yale-Brown Obsessive-Compulsive Scale; Gilles de la Tourette Syndrome Quality; MADRS: Montgomery and Asberg Rating Scale of Life (GTSS-QOL) scale; Y-BOCS: Yale and Brown Obsessive Compulsive Scale; DBS: deep brain stimulation; CI: confidence interval; SD: standard deviation; RCT: randomized controlled trial; MCS: Mental Component Score; PCS: Physical component Score; SF-36: Short-Form 36 Item Quality of Life Survey.

ª Crossover design

Table 16. Relevance Limitations: RCTs of DBS for Tourette Syndrome

<table>
<thead>
<tr>
<th>Study</th>
<th>Populationª</th>
<th>Interventionª</th>
<th>Comparatorª</th>
<th>Outcomesª</th>
<th>Follow-Upª</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kefalopoulou et al (2015)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.3 months of follow-up</td>
</tr>
<tr>
<td>Welter et al (2017)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.3 months of follow-up</td>
</tr>
</tbody>
</table>

DBS: deep brain stimulation; RCT: randomized controlled trial.
The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

- **Population key**: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

- **Intervention key**: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

- **Comparator key**: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

- **Outcomes key**: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

- **Follow-up key**: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

### Table 17. Study Design and Conduct Limitations: RCTs of DBS for Tourette Syndrome

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocationa</th>
<th>Blindingb</th>
<th>Selective Reportingd</th>
<th>Data Completenessd</th>
<th>Powerd</th>
<th>Statisticalfd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Welter et al (2017)</td>
<td></td>
<td></td>
<td></td>
<td>3: Powered to detect a 30 point reduction in YGTSS in active DBS group</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DBS: deep brain stimulation; RCT: randomized controlled trial; YGTSS: Yale-Brown Obsessive-Compulsive Scale; Gilles de la Tourette Syndrome Quality.

OBSERVATIONAL STUDIES

Martinez-Ramirez et al (2018) reported prospective data from the International Deep Brain Stimulation Database and Registry including 185 consecutive patients with refractory TS who were treated with DBS between 2012 and 2016 at 31 sites in 10 countries in Australia, Europe, Asia and North America. Sixty-four percent of the patients had comorbid OCD and 28% had comorbid attention deficit hyperactivity disorder. The population was 78% male. The mean age at diagnosis was 12 years and mean age at surgery was 29 years. Sixty-seven percent received DBS in the centromedian thalamic region, 25% in the aGPi, 15% in the posterior GPi and 3% in the anterior limb of the internal capsule. The YGTSS score improved from a mean (SD) of 75 (18) at baseline to 41 (20) after 1 year of DBS. More than one-third (35%) of patients had adverse events. Two patients (1.3%) suffered intracranial hemorrhage, 4 (3.2%) had infections, 1 (0.6%) had lead explantation.48.

SECTION SUMMARY: Tourette Syndrome

A number of uncontrolled studies, RCTs, and several systematic reviews have been published. Most studies, including the RCTs, had small sample sizes (i.e., ≤15 patients) and used a variety of DBS targets. Two RCTs with 15 or more patients have been reported. One RCT found differences in severity of TS for active vs sham at three months while the other RCT did not. Neither study demonstrated improvements in comorbid symptoms of OCD or depression. Both studies reported high rates of serious adverse events.
Cluster Headache and Facial Pain
Clinical Context and Therapy Purpose
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.

The question addressed in this evidence review is: does DBS improve the net health outcome in patients with cluster headache?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest are patients with cluster headache. 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 are below.

Cluster headaches are primary headaches classified as trigeminal autonomic cephalalgias 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 symptoms or signs, ipsilateral to the headache: conjunctival injection and/or lacrimation; nasal congestion and/or rhinorrhea; eyelid oedema; forehead and facial sweating; miosis and/or ptosis, or; a sense of restlessness or agitation. The diagnostic criteria for episodic cluster headache requires at least two cluster periods lasting from seven days to one year if untreated, and separated by pain-free remission periods of ≥3 months. The diagnostic criteria for chronic cluster headache requires 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 3 times more often than are women.

Interventions
The therapy being considered is DBS.

Comparators
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 attacks 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 nonischemic 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. Steroids 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 headache, trials with sham DBS are most relevant.

Outcomes
The general outcomes of interest are headache intensity and frequency, the effect on function and 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 patients who report more than a 50%, 75% or 100% decrease in headache days per month compared to pre-treatment.

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

**Study Selection Criteria**

1. To assess efficacy outcomes, comparative controlled prospective trials were included, with a preference for RCTs.
2. In the absence of such trials, comparative observational studies, with a preference for prospective studies will be included.
3. To assess long-term outcomes and adverse effects, single arm studies that captured longer periods of follow-up and/or larger populations may be included.
4. Studies with duplicative or overlapping populations will be excluded.

**Randomized Controlled Trials**

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

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

**Section Summary: Cluster Headache and Facial Pain**

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

**Other Neurologic and Psychiatric Disorders**

**Clinical Context and Therapy Purpose**

The role of DBS in treatment of other treatment-resistant neurologic and psychiatric disorders such as major depressive disorders, and OCD, 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.

The question addressed in this evidence review is: does DBS improve the net health outcome in patients with other neurologic and psychiatric disorders?

The following PICOTS were used to select literature to inform this review.

**Patients**

The population of interest are patients with other neurologic and psychiatric disorders such as depression and OCD.
Interventions
The therapy being considered is DBS. Several targets have been investigated.

Comparators
Alternative treatments vary by condition. Sham DBS is an appropriate comparator for RCTs.

Outcomes
Key efficacy outcomes include measures of symptoms severity, functional ability and disability, and QOL.

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

Study Selection Criteria
1. To assess efficacy outcomes, comparative controlled prospective trials were included, with a preference for RCTs.
2. In the absence of such trials, comparative observational studies, with a preference for prospective studies will be included.
3. To assess long-term outcomes and adverse effects, single arm studies that captured longer periods of follow-up and/or larger populations may be included.
4. Studies with duplicative or overlapping populations will be excluded.

Treatment-Resistant Depression
Systematic Reviews
A variety of target areas are being investigated for use of DBS for treatment-resistant depression. A systematic review by Morishita et al (2014) identified 22 published reports with 6 different approaches or targets, including the nucleus accumbens, ventral capsule/ventral striatum, subgenual cingulate cortex, lateral habenula, inferior thalamic nucleus, and medial forebrain bundle. Only three identified studies were controlled with sham stimulation periods, and two multicenter RCTs evaluating subgenual cingulate cortex and ventral striatum/ventral capsule DBS were terminated due to futility (interim analysis demonstrating very low probability of success if the trial was completed as planned). A systematic review by Mosley et al (2015) identified an RCT on DBS for depression; this trial is described next.

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

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

**Section Summary: Treatment-Resistant Depression**

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

**Obsessive-Compulsive Disorder**

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

A meta-analysis by Alonso et al (2015) included studies of any type (including case reports) evaluating DBS for OCD and reporting changes in Y-BOCS score. Reviewers identified 31 studies (total n=116 patients). They did not report study type (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 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 posttreatment Y-BOCS scores). Pooled analysis yielded a global percentage of responders of 60% (95% CI, 49% to 69%). The most frequent adverse events reported were worsening anxiety (25 patients) and hypomanic symptoms (23 patients). Reviewers reported on the benefits and risks of DBS stimulation but could not draw conclusions about stimulation to any particular region or about the safety or efficacy of DBS for OCD compared with sham stimulation or other therapy.

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

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

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

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

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

For individuals who have symptoms (e.g., speech, motor fluctuations) associated with PD (advanced or >4 years in duration with early motor symptoms) who receive DBS of the GPi or STN, the evidence includes RCTs and systematic reviews. The relevant outcomes are symptoms, functional outcomes, QOL, and treatment-related morbidity. One of the systematic reviews (a TEC Assessment) concluded that studies evaluating DBS of the GPi or STN have consistently demonstrated clinically significant improvements in outcomes (e.g., neurologic function). Other systematic reviews have also found significantly better outcomes after DBS than after a control intervention. An RCT in patients with levodopa-responsive PD of at least four years in duration and uncontrolled motor symptoms found that 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 a meaningful improvement in the net health outcome.
For individuals who have primary dystonia who receive DBS of the GPi or STN, the evidence includes systematic reviews, RCTs, and case series. The relevant outcomes are symptoms, functional outcomes, QOL, and treatment-related morbidity. A pooled analysis of 24 studies, mainly uncontrolled, found improvements in motor scores and disability scores after 6 months and at last follow-up (mean, 32 months). Both double-blind RCTs found that severity scores improved more after active than after sham stimulation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have tardive dyskinesia or tardive dystonia who receive DBS, the evidence includes an RCT and case series. The relevant outcomes are symptoms, functional outcomes, QOL, and treatment-related morbidity. Few studies were identified and they had small sample sizes (range, 9-19 patients). The RCT did not report statistically significant improvement in the dystonia severity outcomes or the secondary outcomes related to disability and QOL but may have been under-powered. Additional studies, especially RCTs or other controlled studies, are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have epilepsy who receive DBS, the evidence includes systematic reviews, RCTs and many observational studies. The relevant outcomes are symptoms, functional outcomes, QOL, and treatment-related morbidity. Two RCTs with more than 15 patients were identified. The larger RCT evaluated anterior thalamic nucleus DBS and reported that DBS had a positive impact on seizure frequency during some parts of the blinded trial phase but not others, and a substantial number of adverse events (in >30% of patients). There were no differences between groups in 50% responder rates, LSSS, or QOLUE-31 scores. A seven year open-label follow-up of the RCT included 66% of implanted patients; reasons for missing data were primarily related to adverse events or dissatisfaction with the device. Reduction in seizure frequency continued to improve during follow-up among the patients who continued follow-up. The smaller RCT (n=16) showed a benefit with DBS. Many small observational studies reported fewer seizures compared with baseline, however, without control groups, interpretation of these results is limited. Additional trials are required to determine the impact of DBS on patient outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have TS who receive DBS, the evidence includes observational studies, RCTs and systematic reviews. The relevant outcomes are symptoms, functional outcomes, QOL, and treatment-related morbidity. Two RCTs with 15 or more patients have been reported. One RCT found differences in severity of TS for active vs sham at three months while the other RCT did not. Neither study demonstrated improvements in comorbid symptoms of OCD or depression. Both studies reported high rates of serious adverse events. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have cluster headaches or facial pain who receive DBS, the evidence includes a randomized crossover study and case series. The relevant outcomes are symptoms, functional outcomes, QOL, and treatment-related morbidity. In the randomized study, the between-group difference in response rates did not differ significantly between active and sham stimulation phases. Additional RCTs or controlled studies are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have treatment-resistant depression who receive DBS, the evidence includes RCTs and systematic reviews. The relevant outcomes are symptoms, functional outcomes, QOL, and treatment-related morbidity. The only double-blind, parallel-group RCT in patients with depression did not find that DBS significantly increased the response rate compared with sham; two other RCTs were stopped due to futility. A crossover controlled trial randomized patients to active or to sham stimulation after a year of open-label stimulation. There was a greater reduction in symptom scores after active stimulation but only in patients who were responders in the open-label phase; these findings might not be generalizable. The evidence is insufficient to determine the effects of the technology on health outcomes.
For individuals who have OCD who receive DBS, the evidence includes RCTs and systematic reviews. The relevant outcomes are symptoms, functional outcomes, QOL, and treatment-related morbidity. Among the RCTs on DBS for OC Disorder, only one has reported the outcome of greatest clinical interest (therapeutic response rate), and that trial did not find a statistically significant benefit for DBS compared with sham treatment. The evidence is insufficient to determine the effects of the technology on health.

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

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

Supplemental Information
Clinical Input From Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests from Blue Cross Blue Shield Association, input was received from 2 academic medical centers and 2 physician specialty societies in 2014. Input supported the use of bilateral deep brain stimulation in patients with medically unresponsive tremor in both limbs.

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

American Academy of Neurology
Essential Tremor
The AAN (2011) updated its guidelines on the treatment of essential tremor (ET). This update did not change the conclusions and recommendations of the AAN (2005) practice parameters on DBS for ET. The guidelines stated that bilateral DBS of the thalamic nucleus may be used to treat medically refractory limb tremor in both upper limbs (level C, possibly effective) but that there were insufficient data on the risk/benefit ratio of bilateral vs unilateral DBS in the treatment of limb tremor. There was insufficient evidence to make recommendations on the use of thalamic DBS for head or voice tremor (level U, treatment is unproven).

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

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

**Tardive Syndromes**

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

**European Society for the Study of Tourette Syndrome**

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

**Canadian Network for Mood and Anxiety Treatments**

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

**American Society for Stereotactic and Functional Neurosurgery et al**

The American Society for Stereotactic and Functional Neurosurgery and the Congress of Neurological Surgeons (2014) published a joint systematic review and guidelines on DBS for obsessive-compulsive disorder. The document concluded that there was a single level I study supporting the use of bilateral STN DBS for medically refractory obsessive-compulsive disorder and a single level II study supporting bilateral nucleus accumbens DBS for medically refractory obsessive-compulsive disorder. It also concluded that the evidence on unilateral DBS was insufficient.

**National Institute for Health and Care Excellence**

The NICE has published guidance documents on DBS, as discussed in the following subsections.

**Tremor and Dystonia**

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

**Refractory Chronic Pain Syndromes (Excluding Headache)**

The guidance from NICE (2011) indicated there is evidence that DBS for refractory chronic pain (excluding headache) is associated with serious risks. However, the procedure is “efficacious in some patients” refractory to other treatments. Patients should be informed that DBS may not
control their chronic pain symptoms and that possible risks associated with this procedure include the small risk of death.

**Intractable Trigeminal Autonomic Cephalalgias**

The guidance from NICE (2011) indicated that the evidence on the efficacy of DBS for intractable trigeminal autonomic cephalalgias (e.g., cluster headaches) was “limited and inconsistent, and the evidence on safety shows that there were serious but well-known adverse effects.”

**Refractory Epilepsy**

The guidance from NICE (2012) indicated that the evidence on the efficacy of DBS for refractory epilepsy was limited in both quantity and quality: “The evidence on safety showed that there are serious but well-known adverse effects.”

**Parkinson Disease**

The NICE (2003) stated the evidence on the safety and efficacy of DBS for treatment of PD “appears adequate to support the use of the procedure.” The guidance noted that DBS should only be offered when PD is refractory to best medical treatment.

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**Medicare National Coverage**

Effective for services furnished in April 2003, Medicare covers unilateral or bilateral thalamic ventralis intermedius nucleus DBS for the treatment of ET and/or parkinsonian tremor and unilateral or bilateral STN or globus pallidus interna DBS for the treatment of PD when the following conditions are met:

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

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

1. “Non-idiopathic Parkinson's disease or 'Parkinson's Plus' syndromes.
2. Cognitive impairment, dementia or depression, which would be worsened by or would interfere with the patient's ability to benefit from DBS.
3. Current psychosis, alcohol abuse or other drug abuse.
Structural lesions such as basal ganglionic stroke, tumor or vascular malformation as etiology of the movement disorder.

Previous movement disorder surgery within the affected basal ganglion.

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

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 18.

**Table 18. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td>Treatment in Advanced Parkinson’s Disease: Continuous Intrajejunal Levodopa INfusion VERsus Deep Brain Stimulation</td>
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<td>Dec 2023</td>
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<tr>
<td>NCT01329133</td>
<td>Deep Brain Stimulation and Obsessive-Compulsive Disorder (STOC2)</td>
<td>31</td>
<td>Mar 2020</td>
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<tr>
<td>NCT02076698</td>
<td>Clinical and Medico-economical Assessment of Deep Brain Stimulation of the Anterior Nucleus of the Thalamus for the Treatment of Pharmacoresistant Partial Epilepsy</td>
<td>62</td>
<td>Dec 2019</td>
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<tr>
<td>NCT01973478</td>
<td>Deep Brain Stimulation in Patients With Chronic Treatment Resistant Depression</td>
<td>40</td>
<td>Jan 2020 (suspended)</td>
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<tr>
<td>NCT02535884</td>
<td>Deep Brain Stimulation (DBS) of the Globus Pallidus (GP) in Huntington’s Disease (HD) (HD-DBS)</td>
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<tr>
<td>NCT02937688</td>
<td>Deep Brain Stimulation (DBS) for Parkinson’s Disease International Study (REACH-PD)</td>
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<td>Apr 2021</td>
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<tr>
<td>NCT00354133</td>
<td>The Effect of Deep Brain Stimulation of the Subthalamic Nucleus (STN-DBS) on Quality of Life in Comparison to Best Medical Treatment in Patients With Complicated Parkinson’s Disease and Preserved Psychosocial Competence (EARLYSTIM-study)</td>
<td>251</td>
<td>Mar 2022</td>
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<tr>
<td>NCT01839396</td>
<td>Implantable Neurostimulator for the Treatment of Parkinson’s Disease (INTREPID)</td>
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<tr>
<td>Unpublished</td>
<td>A Clinical Evaluation of Subcallosal Cingulate Gyrus Deep Brain Stimulation for Treatment-Resistant Depression</td>
<td>40</td>
<td>Dec 2017(ongoing)</td>
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<tr>
<td>NCT00640133</td>
<td>Effectiveness of Deep Brain Stimulation for Treating People with Treatment Resistant Obsessive-Compulsive Disorder</td>
<td>27</td>
<td>Feb 2018</td>
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<tr>
<td>NCT01221948</td>
<td>VANTAGE STUDY Vercise™ Implantable Stimulator for Treating Parkinson’s Disease</td>
<td>53</td>
<td>Jun 2018</td>
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<tr>
<td>NCT02583074</td>
<td>Subthalamic Deep Brain Stimulation in Patients With Medication-Refractory Primary Cranial-Cervical Dystonia: A Randomised, Sham-controlled Trial</td>
<td>40</td>
<td>Sep 2017(unknown)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

**References**


**Documentation for Clinical Review**

Please provide the following documentation (if/when requested):

- History and physical including: previous treatment plan and response
- Pharmacological treatment: including type of drug(s), dosage, duration of use, and responses (if applicable)

**Post Service**

- Operative report(s)

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
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<th>Code</th>
<th>Description</th>
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<td>CPT®</td>
<td>61850</td>
<td>Twist drill or burr hole(s) for implantation of neurostimulator electrodes, cortical</td>
</tr>
<tr>
<td>Type</td>
<td>Code</td>
<td>Description</td>
</tr>
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<td>61863</td>
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<td>Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; each additional array (List separately in addition to primary procedure)</td>
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<td>Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array</td>
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<td>61886</td>
<td>Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to 2 or more electrode arrays</td>
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<td>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, cranial nerve, spinal cord, peripheral nerve, or sacral nerve, neurostimulator pulse generator/transmitter, without programming (Code revision effective 1/1/2019)</td>
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<td>Electronic analysis of implanted neurostimulator pulse generator system (e.g., rate, pulse amplitude and duration, battery status, electrode selectability and polarity, impedance and patient compliance measurements), complex deep brain neurostimulator pulse generator/transmitter, with initial or subsequent programming; first hour (Deleted code effective 1/1/2019)</td>
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<td>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. (Code effective 1/1/2019)</td>
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<tr>
<td></td>
<td>L8680</td>
<td>Implantable neurostimulator electrode, each</td>
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<td>L8685</td>
<td>Implantable neurostimulator pulse generator, single array, rechargeable, includes extension</td>
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<td>L8686</td>
<td>Implantable neurostimulator pulse generator, single array, nonrechargeable, includes extension</td>
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<tr>
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<td>L8687</td>
<td>Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension</td>
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<td>Implantable neurostimulator pulse generator, dual array, nonrechargeable, includes extension</td>
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<td>Insertion of Neurostimulator Lead into Brain, Open Approach</td>
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<td>00H03MZ</td>
<td>Insertion of Neurostimulator Lead into Brain, Percutaneous Approach</td>
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<tr>
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<td>00H04MZ</td>
<td>Insertion of Neurostimulator Lead into Brain, Percutaneous Endoscopic Approach</td>
</tr>
<tr>
<td></td>
<td>00H60MZ</td>
<td>Insertion of Neurostimulator Lead into Cerebral Ventricle, Open Approach</td>
</tr>
<tr>
<td></td>
<td>00H63MZ</td>
<td>Insertion of Neurostimulator Lead into Cerebral Ventricle, Percutaneous Approach</td>
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<tr>
<td></td>
<td>00H64MZ</td>
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<td>00HE0MZ</td>
<td>Insertion of Neurostimulator Lead into Cranial Nerve, Open Approach</td>
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<tr>
<td></td>
<td>00HE3MZ</td>
<td>Insertion of Neurostimulator Lead into Cranial Nerve, Percutaneous Approach</td>
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<td>00HE4MZ</td>
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<td>00P00MZ</td>
<td>Removal of Neurostimulator Lead from Brain, Open Approach</td>
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<td>Removal of Neurostimulator Lead from Cranial Nerve, Percutaneous Approach</td>
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Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

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<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
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<tr>
<td>12/18/2009</td>
<td>New policy</td>
<td>Portions of this policy have been derived from the previously existing BSC Medical Policy Bilateral Deep Brain Stimulation for Parkinsons disease and Essential Tremor, and Deep Brain Simulation of the Thalamus for Tremor</td>
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<td>10/29/2010</td>
<td>Coding Update</td>
<td>Medical Policy Committee</td>
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<td>08/07/2013</td>
<td>Policy revision without position change</td>
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<td>02/27/2014</td>
<td>Policy revision without position change</td>
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<td>09/30/2015</td>
<td>Coding Update</td>
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<td>02/01/2016</td>
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<td>Coding update</td>
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Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

**Prior Authorization Requirements (as applicable to your plan)**

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an
Authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.