# Medical Policy

## Title: Deep Brain Stimulation

### Professional

Original Effective Date: March 1, 1985
Revision Date(s): June 1, 1986; October 1, 1994; June 1, 1997; July 1, 1998; June 1, 2006; November 1, 2006; June 13, 2011; September 17, 2013; February 10, 2015; May 24, 2017; January 1, 2019; July 1, 2019; August 21, 2020

Current Effective Date: May 24, 2017

### Institutional

Original Effective Date: April 1, 2007
Revision Date(s): June 13, 2011; September 17, 2013; February 10, 2015; May 24, 2017; January 1, 2019; July 1, 2019; August 21, 2020

Current Effective Date: May 24, 2017

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

### Populations

<table>
<thead>
<tr>
<th>Individuals:</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• With essential tremor or tremor in Parkinson disease</td>
<td>Interventions of interest are: • Deep brain stimulation of the thalamus</td>
<td>Comparators of interest are: • Pharmacologic therapy • Permanent neuroablative procedure (eg, thalamotomy, pallidotomy)</td>
<td>Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related morbidity</td>
</tr>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are: • Deep brain stimulation of the globus pallidus interna or subthalamic nucleus</td>
<td>Comparators of interest are: • Pharmacologic therapy • Physical and speech therapy</td>
<td>Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related morbidity</td>
</tr>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are: • Deep brain stimulation of the globus pallidus interna or subthalamic nucleus</td>
<td>Comparators of interest are: • Pharmacologic therapy • Permanent neuroablative procedure (eg, thalamotomy, pallidotomy)</td>
<td>Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related morbidity</td>
</tr>
<tr>
<td>Populations</td>
<td>Interventions</td>
<td>Comparators</td>
<td>Outcomes</td>
</tr>
<tr>
<td>-------------</td>
<td>---------------</td>
<td>-------------</td>
<td>----------</td>
</tr>
<tr>
<td>Individuals: • With tardive dyskinesia or tardive dystonia</td>
<td>Interventions of interest are: • Deep brain stimulation</td>
<td>Comparators of interest are: • Pharmacologic therapy</td>
<td>Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related morbidity</td>
</tr>
<tr>
<td>Individuals: • With drug refractory epilepsy</td>
<td>Interventions of interest are: • Deep brain stimulation</td>
<td>Comparators of interest are: • Pharmacologic therapy • Vagus nerve stimulation</td>
<td>Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related morbidity</td>
</tr>
<tr>
<td>Individuals: • With multiple sclerosis</td>
<td>Interventions of interest are: • Deep brain stimulation</td>
<td>Comparators of interest are: • Pharmacologic therapy</td>
<td>Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related morbidity</td>
</tr>
<tr>
<td>Individuals: • With Tourette syndrome</td>
<td>Interventions of interest are: • Deep brain stimulation</td>
<td>Comparators of interest are: • Pharmacologic therapy • Cognitive-behavioral therapy</td>
<td>Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related morbidity</td>
</tr>
<tr>
<td>Individuals: • With cluster headaches or facial pain</td>
<td>Interventions of interest are: • Deep brain stimulation</td>
<td>Comparators of interest are: • Pharmacologic therapy • Botulinum toxin • Conservative therapy (eg, diet, exercise)</td>
<td>Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related morbidity</td>
</tr>
<tr>
<td>Individuals: • With treatment-resistant depression</td>
<td>Interventions of interest are: • Deep brain stimulation</td>
<td>Comparators of interest are: • Pharmacologic therapy • Behavioral therapy • Psychotherapy</td>
<td>Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related morbidity</td>
</tr>
<tr>
<td>Individuals: • With obsessive-compulsive disorder</td>
<td>Interventions of interest are: • Deep brain stimulation</td>
<td>Comparators of interest are: • Pharmacologic therapy • Behavioral therapy • Psychotherapy</td>
<td>Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related morbidity</td>
</tr>
<tr>
<td>Individuals: • With anorexia nervosa, alcohol addiction, Alzheimer disease, Huntington disease, or chronic pain</td>
<td>Interventions of interest are: • Deep brain stimulation</td>
<td>Comparators of interest are: • Pharmacologic therapy • Behavioral therapy • Psychotherapy</td>
<td>Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related morbidity</td>
</tr>
</tbody>
</table>

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

**Objective**
The objective of this evidence review is to determine whether deep brain stimulation improves the net health outcome in patients with various conditions such as tremor, epilepsy, dystonia, and depression.
**Background**

**Deep Brain Stimulation**

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

**Regulatory Status**

In 1997, the Activa® Tremor Control System (Medtronic) was cleared for marketing by the U.S. Food and Drug Administration (FDA) for deep brain stimulation. The Activa® Tremor Control System consists of an implantable neurostimulator, a deep brain stimulator lead, an extension that connects the lead to the power source, a console programmer, a software cartridge to set electrical parameters for simulation, 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 originally limited to unilateral implantation for the treatment of tremor, but the indications have evolved over time. In 2002, FDA labeled indications were expanded to include bilateral implantation as a treatment to decrease the symptoms of advanced Parkinson disease not controlled by medication. In 2003, the labeled indications were further expanded to include “…unilateral or bilateral stimulation of the internal globus pallidus or subthalamic nucleus to aid in the management of chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis) in patients seven years of age or above.” In 2018, the deep brain stimulation system received an expanded indication as an adjunctive therapy for epilepsy (P960009 S318). Other deep brain stimulation systems are described in Table 1.

Table 1. Deep Brain Stimulation Systems

<table>
<thead>
<tr>
<th>System</th>
<th>Manufacturer</th>
<th>Features</th>
<th>PMA or HDE</th>
<th>Approval Date</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activa® Deep Brain Stimulation Therapy System</td>
<td>Medtronic</td>
<td></td>
<td>P96009</td>
<td>1997</td>
<td>Unilateral or bilateral stimulation of the internal globus pallidus or subthalamic nucleus for symptoms of Parkinson disease or primary dystonia</td>
</tr>
<tr>
<td>Reclaim® DBS Therapy for Obsessive Compulsive Disorder</td>
<td>Medtronic</td>
<td>Approved for OCD</td>
<td>H050003</td>
<td>2009</td>
<td>Bilateral stimulation of the anterior limb of the internal capsule for severe obsessive-compulsive disorder</td>
</tr>
<tr>
<td>System</td>
<td>Manufacturer</td>
<td>Features</td>
<td>PMA or HDE</td>
<td>Approval Date</td>
<td>Indications</td>
</tr>
<tr>
<td>-------------------------</td>
<td>--------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>------------</td>
<td>--------------</td>
<td>---------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Brio Neurostimulation System</td>
<td>St. Jude Medical</td>
<td></td>
<td>P140009</td>
<td>2015</td>
<td>Parkinsonian tremor (subthalamic nucleus) and essential tremor (thalamus)</td>
</tr>
<tr>
<td>Infinity DBS</td>
<td>St. Jude Medical</td>
<td>Directional leads that &quot;steer&quot; current, reducing side effects.</td>
<td>P140009</td>
<td>2016</td>
<td>Parkinsonian tremor</td>
</tr>
<tr>
<td>Vercise DBS System</td>
<td>Boston Scientific</td>
<td>Directional leads</td>
<td>P150031</td>
<td>2017</td>
<td>Moderate-to-advanced levodopa-responsive PD inadequately controlled with medication alone</td>
</tr>
</tbody>
</table>

DBS: deep brain stimulation; HDE: humanitarian device exemption; OCD: obsessive-compulsive disorder; PD: Parkinson disease; PMA: premarket approval

FDA product codes: OLM, PJS, NHL, MHY.

**POLICY**

I. 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’s disease.

II. 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.

III. Unilateral or bilateral deep brain stimulation of the globus pallidus or subthalamic nucleus may be considered **medically necessary** in the following patients:

A. Those with Parkinson’s disease and ALL of the following:
   1. a good response to levodopa
      **AND**
   2. motor complications not controlled by pharmacologic therapy
      **AND**
   3. ONE of the following:
      a) A minimum score of 30 points on the motor portion of the Unified Parkinson Disease Rating Scale when the patient has been without medication for approximately 12 hours **OR**
      b) Parkinson disease for at least 4 years

B. Patients older than 7 years with chronic, intractable (drug-refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis).
IV. Deep brain stimulation is considered experimental/investigational for:
   A. other movement disorders, including but not limited to tardive dyskinesia, multiple sclerosis, and post-traumatic dyskinesia
   B. treatment of chronic cluster headaches
   C. other psychiatric or neurologic disorders, including but not limited to epilepsy, Tourette syndrome, depression, obsessive-compulsive disorder, anorexia nervosa, alcohol addiction, Alzheimer disease, and chronic pain

Policy Guidelines
1. Disabling, medically unresponsive tremor is defined as all of the following:
   a. tremor causing significant limitation in daily activities
   b. inadequate control by maximal dosage of medication for at least 3 months before implant
2. Contraindications to deep brain stimulation include:
   a. patients who are not good surgical risks because of unstable medical problems or because of the presence of a cardiac pacemaker
   b. patients who have medical conditions that require repeated magnetic resonance imaging (MRI)
   c. patients who have dementia that may interfere with the ability to cooperate
   d. patients who have had botulinum toxin injections within the last 6 months

RATIONALE
This evidence review has been updated with searches of the PubMed database. The most recent literature update was performed through March 13, 2020.

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

The question addressed in this evidence review is: Does deep brain stimulation improve the net health outcome in patients with essential tumor or Parkinson disease?

The following PICO was used to select literature to inform this review.

**Patients**
The relevant populations of interest are patients with essential tumor or symptoms associated with Parkinson disease.

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

**Comparators**
Parkinson disease 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 quality of life. Key safety outcomes include death, stroke, depression, cognition infection and other device and procedure related events.

**Review of Evidence**

**Unilateral Stimulation of the Thalamus**
This section was informed by a TEC Assessment (1997) that focused on unilateral deep brain stimulation 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 deep brain stimulation 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 Parkinson disease (45 patients), essential tumor (13 patients), and multiple sclerosis (MS; 10 patients).\(^2\) Forty-eight (71%) patients were assessed at 5 years: 32 with Parkinson disease, 10 with essential tumor, and 6 with multiple sclerosis (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 essential tumor and multiple sclerosis (MS). Neurologic adverse effects were higher after thalamotomy. Subjective assessments favored stimulation.

Hariz et al (2008) evaluated outcomes of thalamic deep brain stimulation in patients with tremor-predominant Parkinson disease 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.\(^3\)

**Bilateral Stimulation of the Thalamus**

Putzke et al (2005) reported on a series of 25 patients with essential tumor treated with bilateral deep brain stimulation for management of midline tremor (head, voice, tongue, trunk).\(^4\) Three patients died of unrelated causes; 1 patient was lost to follow-up due to transfer of care, and 1 patient did not have baseline evaluation; these patients were not included in the analysis. Patients were evaluated at baseline (before implantation of second stimulator), and at 1, 3, 6, 12, 24, and 36 months. At 12 months, evaluations were obtained from 76% of patients; at 36 months, 50% of patients were evaluated. The most consistent improvement on the Tremor Rating Scale during both unilateral and bilateral stimulation was found for head and voice tremor. The incremental improvement over unilateral stimulation through the first 12 months of bilateral stimulation was significant (p<0.01). For bilateral stimulation at months 3 and 12, outcome measures were significantly better than unilateral stimulation at month 3 (p<0.05). Small sample size limited analysis at months 24 and 36. Dysarthria was reported in 6 (27%) patients and disequilibrium in 5 (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 deep brain stimulation, 26 of whom had essential tumor; of these patients, 18 had unilateral and 8 had bilateral implantation.\(^5\) Sixteen patients with unilateral and 7 with bilateral stimulators completed at least part of the 5 year follow-up evaluations. Patients with bilateral stimulation had a 78% improvement in mean motor tremor scores in the stimulation on state compared with baseline at 5 year follow-up (p=0.02) and 36% improvement in activities of daily living (ADL) scores. Patients with unilateral stimulation improved by 46% on motor tremor scores and 51% on activities of daily living (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 deep brain stimulation systems with directional leads are currently available (approved by the U.S. 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 13.6,7,8,9. The studies showed that patients experienced improved tremor scores and improved quality of life. Compared with historical data from conventional deep brain stimulation systems, directional deep brain stimulation 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 deep brain stimulation of the thalamus results in clinically significant tremor suppression and that outcomes after deep brain stimulation were at least as good as thalamotomy. Subsequent studies reporting long-term follow-up have supported the conclusions of the TEC Assessment and found that tremors were effectively controlled 5 to 6 years after deep brain stimulation. A new technology in deep brain stimulation systems, using directional leads, has more recently emerged.

**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 deep brain stimulation of the internal segment of the globus pallidus interna and subthalamic nucleus for a broader range of Parkinson disease symptoms.10 The Assessment concluded:

- A wide variety of studies have consistently demonstrated that deep brain stimulation of the globus pallidus interna or subthalamic nucleus results in significant improvements, as measured by standardized rating scales of neurologic function. The most frequently observed improvements consist of increased waking hours spent in a state of mobility without dyskinesia, improved motor function during “off” periods when levodopa is not effective, reduction in frequency and severity of levodopa-induced dyskinesia during periods when levodopa is working (“on” periods), improvement in cardinal symptoms of Parkinson disease during periods when medication is not working, and in the case of bilateral deep brain stimulation of the subthalamic nucleus, reduction in the required daily dosage of levodopa and/or its equivalents. The magnitude of these changes 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.
• Deep brain stimulation possesses advantages to other treatment options. Compared with pallidotomy, Deep brain stimulation 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 deep brain stimulation plus medication with medication alone (or plus sham deep brain stimulation) on Parkinson disease outcomes.\textsuperscript{11} Six RCTs (total n=1,184 patients) were included in the review. Five trials exclusively involved bilateral stimulation to the subthalamic nucleus and, in the sixth trial, half of the patients received stimulation to the subthalamic nucleus and the other half had stimulation to the globus pallidus interna. Motor function assessment was blinded in 2 trials and the randomization method was described in 4 trials. Five studies reported motor function, measured by the Unified Parkinson’s Disease Rating Scale-III. In the off-medication phase, motor function was significantly higher with deep brain stimulation 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 deep brain stimulation 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 (eg, activities of daily living (ADLs), quality of life, dementia, depression) also favored the deep brain stimulation 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 Parkinson disease who had failed medical management.\textsuperscript{12} 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 Unified Parkinson’s Disease Rating Scale-II (decrease of 13.35 points out of 52). There was a 28-point decrease in the Unified Parkinson’s Disease Rating Scale-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 Unified Parkinson’s Disease Rating Scale-II and -III scores. The analysis found a 56% reduction in medication use, a 69% reduction in dyskinesia, and a 35% improvement in quality of life with subthalamic stimulation.

A meta-analysis by Appleby et al (2007) found that the rate of suicidal ideation and suicide attempts associated with deep brain stimulation for Parkinson disease ranged from 0.3% to 0.7%.\textsuperscript{13} The completed suicide rate ranged from 0.16% to 0.32%. In light of the rate of suicide in patients treated with deep brain stimulation, reviewers argued for prescreening for suicide risk.

**Parkinson Disease With Early Motor Complications**

Schuepbach et al (2013) published an RCT evaluating deep brain stimulation in patients with Parkinson disease and early motor complications.\textsuperscript{14} 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 Parkinson disease severity below stage 3 in the on-medication condition. A total of 251 patients enrolled, 124 of whom were assigned to deep brain stimulation 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 quality of life. Mean baseline scores on the Parkinson Disease Questionnaire were...
30.2 in the deep brain stimulation plus medical therapy group and 30.2 in the medical therapy only group. At 2 years, the mean score increased by 7.8 points in the deep brain stimulation 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 deep brain stimulation plus medical therapy group (p<0.01 on each): severity of motor signs, ADLs, severity of treatment-related complications, and the number of hours with good mobility and no troublesome dyskinesia. The first 3 secondary outcomes were assessed using Unified Parkinson’s Disease Rating Scale subscales. Regarding medication use, the levodopa-equivalent daily dose was reduced by 39% in the deep brain stimulation plus medical therapy group and increased by 21% in the medical therapy only group.

Sixty-eight patients in the deep brain stimulation 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 deep brain stimulation group that were surgery- or device-related; reoperation was necessary in 4 patients.

**Globus Pallidus Interna versus Subthalamic Nucleus Stimulation**

A number of meta-analyses have compared the efficacy of globus pallidus interna with subthalamic nucleus stimulation in Parkinson disease patients. The meta-analysis by Tan et al (2016) included only RCTs comparing the 2 types of stimulation in patients with advanced Parkinson disease and considered a range of outcomes. This review included RCTs evaluating patients with Parkinson disease who were responsive to levodopa, had at least 6 months of follow-up, and reported at least one of the following outcome measures: Unified Parkinson’s Disease Rating Scale-III, Beck Depression Inventory-II (BDI-II), levodopa-adjusted dose, neurocognitive status, or quality of life. Ten RCTs met eligibility criteria and were included in the quantitative synthesis. After 6 months, there were no significant differences in the Unified Parkinson’s Disease Rating Scale-III scores between the globus pallidus interna and subthalamic nucleus groups for patients in the off-medication/on-stimulation 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 Unified Parkinson’s Disease Rating Scale-III score. In a pooled analysis of the levodopa-adjusted dose, there was a significant difference between the globus pallidus interna and subthalamic nucleus groups, favoring subthalamic nucleus (6 studies; MD=0.60; 95% CI, 0.46 to 0.74). However, the analysis of Beck Depression Inventory II (BDI-II) scores favored the globus pallidus interna 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 Parkinson disease.

**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 deep brain stimulation of the globus pallidus interna or subthalamic nucleus have consistently demonstrated clinically significant improvements in outcomes (eg, neurologic function). Other systematic reviews have also found significantly better outcomes after deep brain stimulation than after a control intervention. One RCT compared deep brain stimulation plus medical therapy with medical therapy alone in patients with levodopa-responsive Parkinson disease of at least 4 years in duration and uncontrolled motor symptoms. The trial found that quality of life at 2 years (eg, motor disability, motor complications) was significantly higher when deep brain stimulation was added to medical therapy. Meta-analyses of
RCTs comparing globus pallidus interna and subthalamic nucleus 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**
Deep brain stimulation 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.

Deep brain stimulation for the treatment of primary dystonia received FDA approval through the humanitarian device exemption process in 2003. The humanitarian device exemption approval process is available for conditions that affect fewer than 4,000 Americans per year. According to this approval process, the manufacturer is not required to provide definitive evidence of efficacy but only probable benefit. The approval was based on the results of deep brain stimulation in 201 patients represented in 34 manuscripts. Three studies reported at least 10 cases of primary dystonia. In these studies, clinical improvement with deep brain stimulation 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 deep brain stimulation improve the net health outcome in patients with primary or secondary dystonia?

The following PICO was 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 (ie, botulinum toxin) and destructive surgical or neurosurgical interventions (ie, 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. Deep brain stimulation 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 or Toronto Western Spasmodic Torticollis Rating scale and quality of life.

The Burke-Fahn-Marsden Dystonia Rating Scale 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 Burke-Fahn-Marsden Dystonia Rating Scale total score.

Toronto Western Spasmodic Torticollis Rating scale is most commonly used to assess the status of people with cervical dystonia. The Toronto Western Spasmodic Torticollis Rating scale 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
Review of Evidence
Systematic Reviews
Moro et al (2017) published a systematic review of literature published through November 2015 on primary dystonia (also known as isolated dystonia).23, Reviewers included studies with at least ten cases. Fifty-eight articles corresponding to 54 unique studies were identified; most involved bilateral deep brain stimulation of the globus pallidus interna. 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.24,

Randomized Controlled Trials
The 2 RCTs identified in the systematic reviews are described in Tables 2-5. Kupsch et al (2006) randomized 40 patients with primary segmental or generalized dystonia to deep brain stimulation or sham stimulation for 3 months.25, The primary outcome was change from baseline to 3 months in the severity of symptoms measured by the Burke-Fahn-Marsden Dystonia Rating Scale assessed by blinded reviewers from videotaped sessions. All patients subsequently received open-label deep brain stimulation for six months after blinded treatment. Results are shown in Table 2. In brief, the change from baseline in the mean Burke-Fahn-Marsden Dystonia Rating Scale movement score was significantly greater in the deep brain stimulation group.

The Volkmann et al (2014) RCT was patient- and observer-blinded evaluation of pallidal neurostimulation in subjects with refractory cervical dystonia.26, The primary outcome was change in the Toronto Western Spasmodic Torticollis Rating scale severity score at the end of the blinded study period (3 months); thereafter, all patients received open-label active stimulation. Results are shown in Table 3. There was significantly greater improvement in the neurostimulation group than in the sham group on the Toronto Western Spasmodic Torticollis Rating scale disability score and...
the Bain Tremor Scale score but not on the Toronto Western Spasmodic Torticollis Rating scale pain score or the Cranio cervical Dystonia Questionnaire-24 score. During the 3 month blinded study period, 22 adverse events were reported in 20 (63%) patients in the neurostimulation group and 13 adverse events were reported in 12 (40%) patients in the sham group. Of these 35 adverse events, 11 (31%) were serious. Additionally, 40 adverse events, 5 of which were serious, occurred during 9 months of the open-label extension period. During the study, 7 patients experienced dysarthria (ie, slightly slurred speech), which was not reversible in 6 patients.

Table 2. Characteristics of RCTs of Deep Brain Stimulation 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);25, 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 GPI DBS  N=20 Sham</td>
</tr>
<tr>
<td>Volkmann (2014)26; 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, ≥15 on the TWSTRS, and an unsatisfactory response to botulinum toxin injection and oral medication.</td>
<td>N=32 GPI DBS  N=30 Sham</td>
</tr>
</tbody>
</table>

DBS: deep brain stimulation; GPI: globuspallidusinternus; TWSTRS: Toronto Western Spasmodic Torticollis Rating Scale; RCT: randomized controlled trial.

Table 3. Results of RCTs of Deep Brain Stimulation for Primary Dystonia

<table>
<thead>
<tr>
<th>Study</th>
<th>Dystonia severity</th>
<th>Disability</th>
<th>Quality of life</th>
<th>Depression</th>
<th>Symptoms</th>
<th>Serious Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kupsch (2006)25</td>
<td>Change in BFMDRS movement at 3 months, Mean (SD)</td>
<td>Change in BFMDRS disability at 3 months, Mean (SD)</td>
<td>Change in SF-36 at 3 months, Mean (SD)</td>
<td>Change in BDI at 3 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>40</td>
<td>39</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)MCS: 5.2 (15.0)</td>
<td>-5.1 (8.4)</td>
<td></td>
<td>3 (8%)3 related to lead dislodgement or 1 related to infection requiring hospitalization</td>
</tr>
<tr>
<td>Sham</td>
<td>-1.4 (3.8)</td>
<td>0.8 (1.2)</td>
<td>PCS: 3.8 (8.4)MCS: 0.2 (8.7)</td>
<td>-0.5 (10.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment effect (95% CI)</td>
<td>MD = 14.40 (8.0 to 20.80); p&lt;0.01</td>
<td>MD = 3.10 (1.72 to 4.48)</td>
<td>PCS MD = 6.30 (1.06 to 11.54)MCS MD = 5.00 (-2.14 to 12.14)</td>
<td>MD = 4.60 (-2.06 to 11.26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volkmann (2014)26</td>
<td>Change in TWSTRS severity at 3 months</td>
<td>Change in TWSTRS disability at 3 months</td>
<td>Change in SF-36 at 3 months</td>
<td>Change in BDI at 3 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>62</td>
<td>61</td>
<td>57</td>
<td>61</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 4. Study Relevance Limitations: RCTs of Deep Brain Stimulation 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)²⁵</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1: Only 3 months of double-blind study</td>
</tr>
<tr>
<td>Volkmann (2014)²⁶</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1: Only 3 months of double-blind study</td>
</tr>
</tbody>
</table>

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

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations 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 5. Study Design and Conduct Limitations: RCTs of Deep Brain Stimulation 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)²⁵</td>
<td></td>
<td>1: Registered after enrollment was complete</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volkmann (2014)²⁶</td>
<td></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>
</tr>
</tbody>
</table>
Deep Brain Stimulation

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


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 deep brain stimulation for primary dystonia. There are numerous small case series and 2 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
Review of Evidence
Randomized Controlled Trials
One RCT has been conducted of pallidal deep brain stimulation in patients with tardive dystonia. Characteristics are shown in Table 6 and results are in Table 7. Briefly, Gruber et al (2018) assessed dystonia/dyskinesia severity using the Burke-Fahn-Marsden Dystonia Rating Scale at 3 months between active vs sham deep brain stimulation. 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. Study limitations are described in Tables 8 and 9.

Table 6. Characteristics of RCTs of Deep Brain Stimulation for Tardive Dyskinesia and Tardive 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>Gruber 2018; Gruber et al 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 Pallidal DBS</td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial; DBS: deep brain stimulation.
Table 7. Results of RCTs of Deep Brain Stimulation 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 2018²⁷</td>
<td>Change in BFMDRS</td>
<td>Change in BFMDRS</td>
<td>Change in SF-36</td>
<td>HAM-D at 3 mon, Mean (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Movement score at 3 mon, Mean (SD)</td>
<td>Disability score at 3 mon, Mean (SD)</td>
<td>at 3 mon, Mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>25</td>
<td>25</td>
<td>24</td>
<td>24</td>
<td>3 events (episodes of confusion, worsening of dystonia following gastrointestinal infection, skin erosion)</td>
</tr>
<tr>
<td>DBS</td>
<td>-5.6 (9.1)</td>
<td>0.5 (5.5)</td>
<td>PCS: 5.4 (10.0)</td>
<td>MCS: 0.5 (10.9)</td>
<td></td>
</tr>
<tr>
<td>Sham</td>
<td>-5.9 (13.9)</td>
<td>-0.3 (1.2)</td>
<td>PCS: 1.6 (7.8)</td>
<td>MCS: -0.6 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Treatment effect (95% CI)</td>
<td>p=0.72</td>
<td>p=0.43</td>
<td>PCS: p=0.17MCS: p=0.53</td>
<td>p=0.69</td>
<td></td>
</tr>
</tbody>
</table>

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 8. Study Relevance Limitations: RCTs of Deep Brain Stimulation for Tardive Dyskinesia and Tardive Dystonia

<table>
<thead>
<tr>
<th>Study</th>
<th>Population²⁷</th>
<th>Intervention²⁷</th>
<th>Comparator²⁷</th>
<th>Outcomes²⁷</th>
<th>Follow-Up²⁷</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gruber 2018</td>
<td>Population unclear; Clinical context is unclear; Study population is unclear; Study population not representative of intended use.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intervention not clearly defined; Version used unclear; Delivery not similar intensity as comparator; Not the intervention of interest.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comparator not clearly defined; Not standard or optimal; Delivery not similar intensity as intervention; Not delivered effectively.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Outcomes not established and validated; Clinical significant difference not prespecified; Clinical significant difference not supported.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Follow-Up not sufficient duration for benefit; Not sufficient duration for harms.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

Table 9. Study Design and Conduct Limitations: RCTs of Deep Brain Stimulation for Tardive Dyskinesia and Tardive Dystonia

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation²⁷</th>
<th>Blinding²⁷</th>
<th>Selective Reporting²⁷</th>
<th>Data Completeness²⁷</th>
<th>Power²⁷</th>
<th>Statistical²⁷</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gruber 2018</td>
<td>Study powered to include 48 patients but only 25 patients enrolled</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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


²⁶ 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).

²⁷ Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

²⁸ 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.

**Case Series**

Stimulation of the globus pallidus interna 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). 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, quality of life, and mood in a series of 9 patients treated with deep brain stimulation of the globus pallidus interna for tardive dystonia were reported by Gruber et al (2009). One week, and 3 to 6 months after surgery, Burke-Fahn-Marsden Dystonia Rating Scale motor scores were improved by 56.4% and 74.1%, Burke-Fahn-Marsden Dystonia Rating Scale 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), Burke-Fahn-Marsden Dystonia Rating Scale motor scores were reduced compared with presurgical assessment by 83%, Burke-Fahn-Marsden Dystonia Rating Scale 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 pharmacoresistant tardive dyskinesia treated with deep brain stimulation. 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 deep brain stimulation to treat tardive syndromes consists of an RCT with 3 months of blinded follow-up and case series with follow-up of 6 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 quality of life for deep brain stimulation 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 deep brain stimulation 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 deep brain stimulation improve the net health outcome in patients with epilepsy?

The following PICO was 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. 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 deep brain stimulation. 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 quality of life. 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.

Review of Evidence
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 deep brain stimulation for multifocal epilepsy (n=109, see discussion in following section), 1 trial on centromedian thalamic deep brain stimulation for multifocal or generalized epilepsy (n=7), and 3RCTs on hippocampal deep brain stimulation for medial temporal lobe
epilepsy (n=15). Meta-analyses provided estimates by site of stimulation. The RCT using anterior thalamic nucleus deep brain stimulation will be discussed in the following section.

Two systematic reviews on the use of deep brain stimulation 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 deep brain stimulation 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 10 and results are in Table 11. Tables 12 and 13 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 3 antiepileptic drugs must have failed to produce adequate seizure control before baseline, with 1 to 4 antiepileptic drugs used at the time of study entry. Patients were asked to keep a daily seizure diary during treatment. All patients received deep brain stimulation 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, quality of life/IE-31 scores, but data were not shown. Data for these outcomes are available in the FDA Summary of Safety and Effectiveness, see Table 10.

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

Cukiert et al (2017) conducted a double-blind, placebo-controlled randomized trial evaluating 16 patients with refractory temporal lobe epilepsy (see Table 9). All patients underwent deep brain stimulation device implantation, and were followed for 6 months. Patients were seen weekly to receive the treatment or placebo. To maintain double-blind status, programming was performed...
by a nontreating assistant. Patients kept a seizure diary during the study period. Patients were considered seizure-free if no seizures occurred during the last 2 months of the trial. Responders were defined as patients experiencing a reduction of 50% or more in frequency reduction. Results are summarized in Table 9.

Table 10. 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)⁶⁶;</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>Troster et al (2017)⁸⁸;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No stimulation (n=55)</td>
</tr>
<tr>
<td>SANTE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cukiert et al (2017)³⁹,</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>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Weekly impedance testing, no stimulation (n=8)</td>
</tr>
</tbody>
</table>

NR: not reported; RCT: randomized controlled trial; V: volts; SANTE: Stimulation of the Anterior Nuclei of the Thalamus for Epilepsy.

Table 11. 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</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>
<td></td>
<td>1 Month</td>
<td>2 Months</td>
<td>3 Months</td>
<td>Mean (SD) annual hospitalizations per patient</td>
<td>Change (SD) in LSSS</td>
<td>Change (SD) in QOLIE-31</td>
<td></td>
</tr>
<tr>
<td>Troster et al (2017)⁸⁸;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SANTE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBS</td>
<td>30%⁹</td>
<td>0.08 (0.56)⁹</td>
<td>22%⁹</td>
<td>-8.2 (17.8)⁹</td>
<td>2.5 (8.7)⁹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham</td>
<td>26%⁹</td>
<td>0.37 (1.17)⁹</td>
<td>22%⁹</td>
<td>-6.8 (19.6)⁹</td>
<td>2.8 (8.0)⁹</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=0.83⁹</td>
<td>p=0.11⁹</td>
<td>p=0.87⁹</td>
<td>p=0.55⁹</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 months: higher rate of depression and memory adverse events in treatment group (difference disappeared in long-term follow-up)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FIAS at 6 Months
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 quality of life and functional outcomes in the publications although SANTE outcomes are available in the FDA Summary of Safety and Effectiveness. Cukiert et al (2017) did not include information on power/sample size, flow of participants and missing data.

### Table 12. Study Relevance Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Population(^a)</th>
<th>Intervention(^b)</th>
<th>Comparator(^c)</th>
<th>Outcomes(^d)</th>
<th>Follow-Up(^e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher et al (2010)(^36,36;) SANTE</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>Cukiert et al (2017)(^39)</td>
<td></td>
<td></td>
<td></td>
<td>1. Quality of life and functional outcomes not reported</td>
<td></td>
</tr>
</tbody>
</table>

SSED: Summary of Safety and Effectiveness; SANTE: Stimulation of the Anterior Nuclei of the Thalamus for Epilepsy.

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

\(^a\) 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.

\(^b\) Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

\(^c\) Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

\(^d\) 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.

\(^e\) Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.
Table 13. Study Design and Conduct Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocationa</th>
<th>Blindingb</th>
<th>Selective Reportingc</th>
<th>Data Completenessd</th>
<th>Powere</th>
<th>Statisticalf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher et al (2010)36; SANTE</td>
<td></td>
<td></td>
<td>2. Several seizure outcomes as well as quality of life collected but not reported in publication; available in SSED.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cukiert et al (2017)39</td>
<td></td>
<td></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>2: Not clear if analyses were done independently for each time point or if analyses adjusted for multiple observations4: Comparative treatment effects not calculated</td>
<td></td>
</tr>
</tbody>
</table>

SSED: Summary of Safety and Effectiveness; SANTE: Stimulation of the Anterior Nuclei of the Thalamus for Epilepsy.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations 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.

Observational Studies

Long-term outcomes of the SANTE trial were reported by Salanova et al (2015).40 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 leads 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 7 year follow-up of SANTE was reported in the FDA Summary of Safety and Effectiveness (Table 14).37 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). quality of lifeIE-31 scores (n=67) improved by a mean of 4.9 (SD=11) points at year 7. Liverpool Seizure Severity Scale 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 deep brain stimulation, 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 14. 7-Year Outcomes from SANTEa

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>N</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>
<td></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>
<td></td>
</tr>
</tbody>
</table>

LSSS: Liverpool Seizure Severity Scale; QOLIE-31: Quality of Life in Epilepsy Score; SD: standard deviation; BL: baseline; SANTE: Stimulation of the Anterior Nuclei of the Thalamus for Epilepsy.

a 110 patients were implanted with DBS in SANTE

b -39% assuming worst case for missing data.

Kim et al (2017) conducted a retrospective chart review of 29 patients with refractory epilepsy treated with deep brain stimulation.141 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 deep brain stimulation 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 3 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 3 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, Liverpool Seizure Severity Scale, or quality of lifeIE-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 7 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. Deep brain stimulation 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 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 Tourette
Syndrome 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 deep brain stimulation improve the net health outcome in patients with Tourette Syndrome?

The following PICO was used to select literature to inform this review.

**Patients**
The population of interest are patients with Tourette Syndrome who have disabling tics that are refractory to optimal medical management.

**Interventions**
The therapy being considered is deep brain stimulation. Several targets have been investigated such as the medial thalamus at the crosspoint of the centromedian nucleus, substantiaperventricularis, and nucleus ventro-oralisinternus, subthalamic nucleus, caudate nucleus, globus pallidus interna, and the anterior limb of the internal capsule and nucleus accumbens.

**Comparators**
Intervention may be initiated when symptoms of Tourette Syndrome 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), functional ability and disability, medication use and quality of life. The overall score for the Yale Global Tic Severity Scale 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.

**Review of Evidence**

**Systematic Reviews**
Several systematic reviews of the literature on deep brain stimulation for Tourette Syndrome have been published. Most recent systematic reviews (ie, those published in 2015-2017) qualitatively described the literature. Only Baldermann et al (2016) conducted pooled analyses of
study data.\textsuperscript{42} That review identified 57 studies on deep brain stimulation for Tourette Syndrome, 4 of which were randomized crossover studies. The studies included a total of 156 cases. Twenty-four studies included a single patient and 4 had sample sizes of 10 or more (maximum, 18 patients). Half of the patients (n=78) received thalamus stimulation and the next most common areas of stimulation were the globus pallidus interna anteromedial part (n=44) and post ventrolateral part (n=20). Two of the RCTs used thalamic stimulation, one used bilateral globus pallidus stimulation, and one used both. The primary outcome was the Yale Global Tic Severity Scale. In a pooled analysis of within-subject pre-post data, there was a median improvement of 53\% in Yale Global Tic Severity Scale 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 Yale Global Tic Severity Scale score and 54\% showed improvements of 50\% or more. In addition, data were pooled from the 4 crossover RCTs: 27 patients received deep brain stimulation 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 deep brain stimulation (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.

\textit{Randomized Controlled Trials}

Trials including 15 patients or more will be described in more detail in this section. Study characteristics are shown in Table 15 and results are shown in Table 16. Study limitations are described in Tables 17 and 18.

The crossover RCT was published by Kefalopoulou et al (2015).\textsuperscript{47} The double-blind trial included 15 patients with severe medically refractory Tourette syndrome; all received bilateral globus pallidus interna surgery for deep brain stimulation and were randomized to the off-stimulation phase first or the on-stimulation phase first for 3 months, followed by the opposite phase for the next 3 months. Of the 15 receiving surgery, 14 were randomized and 13 completed assessments after both on and off phases. For the 13 trial completers, mean Yale Global Tic Severity Scale scores were 80.7 in the off-stimulation phase and 68.3 in the on-stimulation phase. The mean difference in Yale Global Tic Severity Scale 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 Yale Global Tic Severity Scale 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 globus pallidus interna deep brain stimulation in 17 adults with severe Tourette Syndrome.\textsuperscript{48} The primary endpoint was difference in Yale Global Tic Severity Scale score between the beginning and end of the 3 month double-blind period. The study was powered to detect a benefit amounting to a 30-point reduction in Yale Global Tic Severity Scale score in the active deep brain stimulation group and may, therefore, have been underpowered to detect smaller changes in Yale Global Tic Severity Scale. There was no significant differences in Yale Global Tic Severity Scale score change between groups (active deep brain stimulation median change 1.1\% [interquartile range –23.9 to 38.1] vs sham deep brain stimulation 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 quality of life. 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 15. Characteristics of RCTs of Deep Brain Stimulation for Tourette Syndrome

<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)⁴⁷, NCT01647269</td>
<td>United Kingdom</td>
<td>2</td>
<td>2009 to 2013</td>
<td>Adults with Tourette Syndrome 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 interna DBS) Stimulation off</td>
</tr>
<tr>
<td>Welter et al (2017)⁴⁸, NCT00478842</td>
<td>France</td>
<td>8</td>
<td>2007 to 2012</td>
<td>Adults aged 18–60 years with severe, medically refractory TS N=8 anterior internal globus pallidus DBS</td>
<td>N= 9 Sham DBS</td>
</tr>
</tbody>
</table>

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

### Table 16. Results of RCTs of Deep Brain Stimulation 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)⁴⁷, a</td>
<td>YGTSS, Mean (SD) at 3 months</td>
<td>Y-BOC, Mean (SD) at 3 months</td>
<td>GTS-QOL, Mean (SD) at 3 months</td>
<td>Beck Depression Inventory, Mean (SD) at 3 months</td>
<td></td>
</tr>
<tr>
<td>N 15⁴⁷</td>
<td>15⁴⁷</td>
<td>15⁴⁷</td>
<td>15⁴⁷</td>
<td>15⁴⁷</td>
<td></td>
</tr>
<tr>
<td>DBS 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>
<td></td>
</tr>
<tr>
<td>No stimulation 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>
<td></td>
</tr>
<tr>
<td>Treatment effect (95% CI)  12.4 (0.1–24.7, p=0.05)</td>
<td>p=0.98</td>
<td>p=0.04</td>
<td>p=0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Welter et al (2017)⁴⁸, a</td>
<td>YGTSS, Mean change (CI) at 3 months</td>
<td>Y-BOC, 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 16</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>DBS -4.5 (-12.5 to 0.5)</td>
<td>-3.5 (-6.8 to 0.3)</td>
<td>PCS 6.1 (1.2 to 8.7): MCS: 10.1 (1.8 to 16.8):</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>
<td></td>
</tr>
</tbody>
</table>
Study & Tic severity & Co-morbid symptoms & Quality of life & Depression symptoms & Serious Adverse Events
---
No stimulation & 5.0 (-2.5 to 17.5) & 0.0 (-1.0 to 0.0) & PCS: -0.4 (-3.1 to 16.1) & MCS: -2.6 (-16.7 to 10.0) & 0.0 (-2.3 to 1.8)
 Treatment effect (95% CI) & p=0.039 & p=0.25 & PCS:p>0.99 & MCS:p=0.14 & p = 0.25

YGTSS: Yale Global Tic Severity Scale; Y-BOCS: Yale and Brown Obsessive Compulsive Scale; GTS-QOL: Gilles de la Tourette Syndrome Quality of Life scale; MADRS: Montgomery and Asberg Rating 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.

Table 17. Study Relevance Limitations: RCTs of Deep Brain Stimulation for Tourette Syndrome

<table>
<thead>
<tr>
<th>Study</th>
<th>Population^a</th>
<th>Intervention^b</th>
<th>Comparator^c</th>
<th>Outcomes^d</th>
<th>Follow-Up^e</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kefalopoulou et al (2015)^47</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1. 3 months of follow-up</td>
</tr>
<tr>
<td>Welter et al (2017)^48</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 study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

^a 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.

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

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

^d 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.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 18. Study Design and Conduct Limitations: RCTs of Deep Brain Stimulation for Tourette Syndrome

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation^a</th>
<th>Blinding^b</th>
<th>Selective Reporting^c</th>
<th>Data Completeness^d</th>
<th>Power^e</th>
<th>Statistical^f</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kefalopoulou et al (2015)^47</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3: Sample size based on &quot;practical considerations&quot;</td>
<td></td>
</tr>
<tr>
<td>Welter et al (2017)^48</td>
<td></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>
</tr>
</tbody>
</table>

DBS: deep brain stimulation; RCT: randomized controlled trial; YGTSS: Yale-Brown Obsessive-Compulsive Scale; Gilles de la Tourette Syndrome Quality.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations 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.

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 Tourette
Syndrome who were treated with deep brain stimulation 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. Fifty-seven percent received deep brain stimulation in the centromedian thalamic region, 25% in the anterior internal globus pallidus, 15% in the posterior globus pallidus interna and 3% in the anterior limb of the internal capsule. The Yale Global Tic Severity Scale score improved from a mean (SD) of 75 (18) at baseline to 41 (20) after 1 year of deep brain stimulation. 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.49,

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 (ie, ≤15 patients) and used a variety of deep brain stimulation targets. Two RCTs with 15 or more patients have been reported. One RCT found differences in severity of Tourette Syndrome for active vs sham at 3 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
Deep brain stimulation 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 deep brain stimulation improve the net health outcome in patients with cluster headache?

The following PICO was 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.50 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 rhinorrhoea; 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 2 cluster periods lasting from 7 days to 1 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 1 year or more without remission, or with remission of less than 3 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 deep brain stimulation.

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 2 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 deep brain stimulation are most relevant.

Outcomes
The general outcomes of interest are headache intensity and frequency, the effect on function and quality of life 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.

Review of Evidence
Randomized Controlled Trials
Fontaine et al (2010) published the results of a prospective crossover, double-blind, multicenter trial in 11 patients who received deep brain stimulation of the posterior hypothalamus for severe refractory chronic cluster headache. The randomized phase compared active with sham stimulation during 1 month periods and was followed by a 1 year open phase. Severity of cluster headache was assessed using the weekly attack frequency (primary outcome), pain intensity, sumatriptan injections, emotional impact, and quality of life (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 deep brain stimulation for the ipsilateral posterior hypothalamus in patients with chronic cluster headache.\textsuperscript{52,53} 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 deep brain stimulation 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 deep brain stimulation in treatment of other treatment-resistant neurologic and psychiatric disorders such as major depressive disorders, and obsessive-compulsive disorder (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 deep brain stimulation 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 deep brain stimulation improve the net health outcome in patients with other neurologic and psychiatric disorders?

The following PICO was 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 deep brain stimulation. Several targets have been investigated. Affective limbic structures include the ventral striatum/ventral capsule, anterior limb of the internal capsule, and subgenual cingulate. Memory implicated structures include the fornix and nucleus basalis.

**Comparators**
Alternative treatments vary by condition. Sham deep brain stimulation is an appropriate comparator for RCTs.

**Outcomes**
Key efficacy outcomes include measures of symptoms severity, functional ability and disability, and quality of life.

Outcomes for major depressive disorder are measured with validated scales, most commonly the Hamilton Depression Rating or the Montgomery-Asberg Depression Rating Scale. Response is
considered a 50% or greater reduction in symptoms, while remission is based on achieving a specific threshold on one of the scales.

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**

**Review of Evidence**

**Systematic Reviews**

A variety of target areas are being investigated for use of deep brain stimulation for treatment resistant depression. A systematic review by Morishita et al (2014) identified 22 published reports with 6 different approaches or targets, including the nucleus accumbens, ventral capsule/ventral striatum, subgenual cingulate cortex, lateral habenula, inferior thalamic nucleus, and medial forebrain bundle. Only 3 identified studies were controlled with sham stimulation periods, and 2 multicenter RCTs evaluating subgenual cingulate cortex and ventral striatum/ventral capsule deep brain stimulation 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 deep brain stimulation for depression; this trial is described next.

**Controlled Trials**

**Ventral Capsule/Ventral Striatum**

An industry-sponsored, double-blind RCT evaluating deep brain stimulation 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) deep brain stimulation, 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 deep brain stimulation of the ventral capsule/ventral striatum is effective for treating treatment-resistant depression.
**Anterior Limb of the Internal Capsule**
A crossover RCT evaluating active and sham phases of deep brain stimulation of the ventral anterior limb of the internal capsule 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 deep brain stimulation 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 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, Hamilton Depression Rating scores were significantly improved at the end of the active stimulation phase (mean Hamilton Depression Rating score, 16.5) compared with the sham stimulation phase (mean Hamilton Depression Rating score, 23.1; p<0.001). Mean Hamilton Depression Rating scores were similar after the active (19.0) and sham phases for initial nonresponders (23.0). Among initial responders, the mean Hamilton Depression Rating 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 deep brain stimulation 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 deep brain stimulation-naive.

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

**Section Summary: Treatment-Resistant Depression**
A number of case series and several prospective controlled trials evaluating deep brain stimulation in patients with treatment resistant depression have been published. Two RCTs of deep brain stimulation in the subgenual cingulate cortex and ventral striatum/ventral capsule were terminated for futility. Another RCT of stimulation of the ventral striatum/ventral capsule 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 sham or active stimulation of the anterior limb of the internal capsule 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. A 2019 sham-controlled within-subject study of stimulation of the subcallosal singulate found prolonged response in 50% of patients and remission in 30% of patients with treatment resistant depression. Deep brain stimulation for patients with major depressive disorder who have failed all other treatment options is an active area of research, but brain regions that might be effective for treatment resistant depression have yet to be established.

**Obsessive-Compulsive Disorder**

Several systematic reviews evaluating deep brain stimulation for OCD have been published.\(^{59,60,61,62,63}\) Two of these reviews included meta-analyses and pooled study findings. Kisely et al (2014) included only double-blind RCTs of active vs sham deep brain stimulation.\(^{62}\) 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 (3 studies), the nucleus accumbens (one study), and the subthalamic nucleus (one study). Duration of treatment ranged from 2 to 12 weeks. All studies reported scores on the Yale-Brown Obsessive Compulsive Scale, 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 Yale-Brown Obsessive Compulsive Scale score of 35% or more from the pretreatment baseline, with a reduction of 25% to 35% considered a partial response. Only 1 of the 5 studies compared the proportion of responders on the Yale-Brown Obsessive Compulsive Scale 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 Yale-Brown Obsessive Compulsive Scale score. When data from the 5 studies were pooled, there was a statistically significant reduction in the mean Yale-Brown Obsessive Compulsive Scale in the active vs the sham group (MD=-8.49; 95% CI, -12.18 to -4.80). The outcome measure, however, does not permit conclusions on whether the between-group difference is clinically meaningful. Trial authors reported 16 serious adverse events including 1 cerebral hemorrhage and 2 infections requiring electrode removal. Additionally, nonserious transient adverse events were reported, including 13 reports of hypomania, 6 of increase in depressive or anxious symptoms, and 6 of headaches.

A meta-analysis by Alonso et al (2015) included studies of any type (including case reports) evaluating deep brain stimulation for OCD and reporting changes in Yale-Brown Obsessive Compulsive Scale score.\(^{61}\) Reviewers identified 31 studies (total n=116 patients). They did not report study type (ie, controlled vs uncontrolled); however, the meta-analysis only included patients who received active treatment. Twenty-four (77%) studies included 10 or fewer patients. Most studies (24, including 83 patients) involved deep brain stimulation of striatal areas. Of the remaining studies, 5 (27 patients) addressed subthalamic nucleus stimulation and 2 (6 patients) addressed stimulation of the inferior thalamic peduncle. Twelve studies provided patient-level data and 4 provided pooled data on percentage of responders (ie, >35% reduction in posttreatment Yale-Brown Obsessive Compulsive Scale 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 deep brain stimulation but could not draw conclusions about stimulation to any particular region or about the safety or efficacy of deep brain stimulation for OCD compared with sham stimulation or other therapy.
**Section Summary: Obsessive-Compulsive Disorder**
The literature on deep brain stimulation 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, a clinically significant change in Yale-Brown Obsessive Compulsive Scale scores. Uncontrolled data have suggested improvements in OCD symptoms after deep brain stimulation treatment but have also identified a substantial number of adverse events. Additional blinded controlled studies are needed to draw conclusions about the impact of deep brain stimulation 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.2 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 deep brain stimulation for this population.

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

**Summary of Evidence**
For individuals who have essential tremor or tremor in Parkinson disease who receive deep brain stimulation of the thalamus, the evidence includes a systematic review and case series. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. The systematic review (a TEC Assessment) concluded that there was sufficient evidence that deep brain stimulation of the thalamus results in clinically significant tremor suppression and that outcomes after deep brain stimulation 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 deep brain stimulation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have symptoms (eg, speech, motor fluctuations) associated with Parkinson disease (advanced or >4 years in duration with early motor symptoms) who receive deep brain stimulation of the globus pallidus interna or subthalamic nucleus, the evidence includes randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. One of the systematic reviews (a TEC Assessment) concluded that studies evaluating deep brain stimulation of the globus pallidus interna or subthalamic nucleus have consistently demonstrated clinically significant improvements in outcomes (eg, neurologic function). Other systematic reviews have also found significantly better outcomes after deep brain stimulation than after a control intervention. An RCT in patients with levodopa-responsive Parkinson disease of at least four years in duration and uncontrolled motor symptoms found that quality of life at two years was significantly higher when deep brain stimulation was provided in addition to medical therapy. Meta-analyses of RCTs comparing deep brain stimulation of the globus pallidus interna with deep brain stimulation of the...
subthalamic nucleus 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 deep brain stimulation of the globus pallidus interna or subthalamic nucleus, the evidence includes systematic reviews, RCTs, and case series. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. A pooled analysis of 24 studies, mainly uncontrolled, found improvements in motor scores and disability scores after 6 months and at last follow-up (mean, 32 months). 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 deep brain stimulation, the evidence includes an RCT and case series. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Few studies were identified and they had small sample sizes (range, 9-19 patients). The RCT did not report statistically significant improvement in the dystonia severity outcomes or the secondary outcomes related to disability and quality of life 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 deep brain stimulation, the evidence includes systematic reviews, RCTs and many observational studies. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Two RCTs with more than 15 patients were identified. The larger RCT evaluated anterior thalamic nucleus deep brain stimulation and reported that deep brain stimulation 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, Liverpool Seizure Severity Scale, or Quality of Life in Epilepsy scores. A 7 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 deep brain stimulation. 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 deep brain stimulation on patient outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have Tourette syndrome who receive deep brain stimulation, the evidence includes observational studies, RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Two RCTs with 15 or more patients have been reported. One RCT found differences in severity of Tourette syndrome for active vs sham at three months while the other RCT did not. Neither study demonstrated improvements in comorbid symptoms of obsessive-compulsive disorder 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 deep brain stimulation, the evidence includes a randomized crossover study and case series. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. In the randomized study, the between-group difference in response rates did not differ significantly between active and sham stimulation phases. Additional RCTs or controlled studies are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have treatment resistant depression who receive deep brain stimulation, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. A number of case series and several prospective controlled trials evaluating deep brain stimulation in patients with have been published. Two RCTs of deep brain stimulation in the subgenual cingulate cortex and ventral striatum/ventral capsule were terminated for futility. Another RCT of stimulation of the same brain area (ventral striatum/ventral capsule) 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 sham or active stimulation of the anterior limb of the internal capsule 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. Stimulation of the subcallosal (subgenual) cingulate was evaluated in a 2019 sham-controlled within-subject study that found prolonged response in 50% of patients and remission in 30% of patients with treatment resistant depression. Deep brain stimulation for patients with major depressive disorder who have failed all other treatment options is an active area of research, but the brain regions that might prove to be effective for treatment resistant depression have yet to be established. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

For individuals who have multiple sclerosis who receive deep brain stimulation, the evidence includes an RCT. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. One RCT with ten multiple sclerosis patients is insufficient evidence on which to draw conclusions about the efficacy of deep brain stimulation 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 deep brain stimulation, the evidence includes case series. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. RCTs are needed to evaluate the efficacy of deep brain stimulation for these conditions. The evidence is insufficient to determine the effects of the technology on health outcomes.
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, input was received from 2 academic medical centers and 2 physician specialty societies while this policy was under review 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
American Academy of Neurology
Essential Tremor
In 2011, the American Academy of Neurology (AAN) updated its guidelines on the treatment of essential tremor.64 This update did not change the conclusions and recommendations of the AAN (2005) practice parameters on deep brain stimulation for essential tremor.65 The guidelines stated that bilateral deep brain stimulation 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 deep brain stimulation in the treatment of limb tremor. There was insufficient evidence to make recommendations on the use of thalamic deep brain stimulation for head or voice tremor (level U, treatment is unproven).

Parkinson Disease
Guidelines from AAN (2006) on the treatment of Parkinson disease with motor fluctuations and dyskinesia found that, although criteria are evolving, patients with Parkinson disease considered candidates for deep brain stimulation include those who are levodopa-responsive, non-demented, and neuropsychiatrically intact patients who have intractable motor fluctuations, dyskinesia, or tremor.66 The AAN concluded that deep brain stimulation of the subthalamic nucleus may be considered a treatment option in Parkinson disease 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 deep brain stimulation 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 Parkinson disease patients.

Guidelines from AAN (2010) on the treatment of nonmotor symptoms of Parkinson disease found insufficient evidence for the treatment of urinary incontinence with deep brain stimulation of the subthalamic nucleus.67 The AAN found that deep brain stimulation of the subthalamic nucleus possibly improves sleep quality in patients with advanced Parkinson disease. However, none of the studies performed deep brain stimulation to treat insomnia as a primary symptom, and deep brain stimulation of the subthalamic nucleus is not currently used to treat sleep disorders.

Tardive Syndromes
Guidelines from AAN on the treatment of tardive syndromes were updated in 2018.68 The latest guidelines state that “pallidal deep brain stimulation 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).
**Tourette Syndrome**

Guidelines from AAN (2019) provide recommendations on the assessment for and use of deep brain stimulation in adults with severe, treatment-refractory tics. AAN notes that patients with severe Tourette syndrome resistant to medical and behavioral therapy may benefit from deep brain stimulation, but there is no consensus on the optimal brain target. Brain regions that have been stimulated in patients with Tourette Syndrome include the centromedian thalamus, the globus pallidus internus (ventral and dorsal), the globus pallidus externus, the subthalamic nucleus, and the ventral striatum/ventral capsular nucleus accumbens region. AAN concludes that deep brain stimulation of the anteromedial globus pallidus is possibly more likely than sham stimulation to reduce tic severity.

**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 deep brain stimulation for obsessive-compulsive disorder. The document concluded that there was a single level I study supporting the use of bilateral subthalamic nucleus deep brain stimulation for medically refractory obsessive-compulsive disorder and a single level II study supporting bilateral nucleus accumbens deep brain stimulation for medically refractory obsessive-compulsive disorder. It also concluded that the evidence on unilateral deep brain stimulation was insufficient.

**Congress of Neurologic Surgeons**

In 2018, evidence-based guidelines from the Congress of Neurologic Surgeons compared the efficacy of bi-lateral deep brain stimulation of the subthalamic nucleus and globus pallidus internus for the treatment of patients with Parkinson disease.

**Table 19. Recommendations of the Congress of Neurologic Surgeons for DBS for Parkinson Disease**

<table>
<thead>
<tr>
<th>Goal</th>
<th>Most Effective Area of Stimulation (subthalamic nucleus or globus pallidus internus)</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improving motor symptoms</td>
<td>subthalamic nucleus or globus pallidus internus are similarly effective</td>
<td>I</td>
</tr>
<tr>
<td>Reducing dopaminergic medication</td>
<td>subthalamic nucleus</td>
<td>I</td>
</tr>
<tr>
<td>Treatment of &quot;on&quot; medication dyskinesias</td>
<td>globus pallidus internus if reduction of medication is not anticipated</td>
<td>I</td>
</tr>
<tr>
<td>Quality of life</td>
<td>no evidence to recommend one over the other</td>
<td>I</td>
</tr>
<tr>
<td>Lessen impact of DBS on cognitive decline</td>
<td>globus pallidus internus</td>
<td>I</td>
</tr>
<tr>
<td>Reduce risk of depression</td>
<td>globus pallidus internus</td>
<td>I</td>
</tr>
<tr>
<td>Reduce adverse effects</td>
<td>insufficient evidence to recommend one over the other</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

**National Institute for Health and Care Excellence**

The United Kingdom's National Institute for Health and Care Excellence (NICE) has published guidance documents on deep brain stimulation, as discussed in the following subsections.
Tremor and Dystonia
In 2006, NICE made the same statements about use of deep brain stimulation 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 subthalamic nucleus, 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)
In 2011, guidance from NICE indicated there is evidence that deep brain stimulation 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 deep brain stimulation 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
In 2011, guidance from NICE indicated that the evidence on the efficacy of deep brain stimulation for intractable trigeminal autonomic cephalalgias (eg, cluster headaches) was “limited and inconsistent, and the evidence on safety shows that there were serious but well-known adverse effects.”

Refractory Epilepsy
In 2012, guidance from NICE indicated that the evidence on the efficacy of deep brain stimulation 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
In 2003, NICE stated that the evidence on the safety and efficacy of deep brain stimulation for treatment of Parkinson disease “appears adequate to support the use of the procedure.” The guidance noted that deep brain stimulation should only be offered when Parkinson disease is refractory to best medical treatment.

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

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 20. Studies with fewer than 20 participants are not included.

Table 20. 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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01521754</td>
<td>Product Surveillance Registry- Deep Brain Stimulation for Epilepsy</td>
<td>191</td>
<td>Mar 2020</td>
</tr>
<tr>
<td>NCT02076698</td>
<td>Deep Brain Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy</td>
<td>62</td>
<td>Jun 2021</td>
</tr>
<tr>
<td>NCT04181229</td>
<td>Deep Brain Stimulation Post Failed Vagal Nerve Stimulation</td>
<td>50</td>
<td>Nov 2022</td>
</tr>
<tr>
<td>NCT No.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
</tr>
<tr>
<td>--------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>--------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>NCT04164056</td>
<td>Hippocampal and Thalamic deep brain stimulation for Bilateral Temporal Lobe Epilepsy</td>
<td>80</td>
<td>Sep 2024</td>
</tr>
<tr>
<td>NCT03900468</td>
<td>Medtronic Deep Brain Stimulation Therapy for Epilepsy Post-Approval Study (EPAS)</td>
<td>216</td>
<td>Mar 2027</td>
</tr>
<tr>
<td>Huntingon's Disease</td>
<td>NCT02535884a Deep Brain Stimulation of the Globus Pallidus (GP) in Huntington's Disease</td>
<td>50</td>
<td>Oct 2020</td>
</tr>
<tr>
<td>Parkinson Disease</td>
<td>NCT02937688a Deep Brain Stimulation for Parkinson's Disease International Study (REACH-PD)</td>
<td>264</td>
<td>Apr 2021</td>
</tr>
<tr>
<td></td>
<td>NCT00354133 The Effect of Deep Brain Stimulation of the Subthalamic Nucleus 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>
</tr>
<tr>
<td></td>
<td>NCT01839396a Implantable Neurostimulator for the Treatment of Parkinson's Disease (INTREPID)</td>
<td>313</td>
<td>Aug 2023</td>
</tr>
<tr>
<td>Obsessive-Compulsive Disorder</td>
<td>NCT01506206 ON/OFF Stimulation and Impulsivity in Patients With Deep Brain Stimulators</td>
<td>60</td>
<td>Dec 2020</td>
</tr>
<tr>
<td></td>
<td>NCT01590862 ON/OFF Stimulation and Reward Motivation in Patients With Deep Brain Stimulators</td>
<td>60</td>
<td>Dec 2020</td>
</tr>
<tr>
<td></td>
<td>NCT00640133 Effectiveness of Deep Brain Stimulation for Treating People With Treatment Resistant Obsessive-Compulsive Disorder</td>
<td>27</td>
<td>Aug 2020</td>
</tr>
<tr>
<td></td>
<td>NCT02773082a Reclaim Deep Brain Stimulation Therapy for Obsessive-Compulsive Disorder (OCD)</td>
<td>50</td>
<td>Apr 2020</td>
</tr>
<tr>
<td></td>
<td>NCT04228744 The Efficacy and Mechanism of deep brain stimulation in VIC and NAcc for Refractory OCD</td>
<td>20</td>
<td>Dec 2022</td>
</tr>
<tr>
<td></td>
<td>NCT02844049 European Study of Quality of Life in Resistant OCD Patients Treated by subthalamic nucleus deep brain stimulation</td>
<td>60</td>
<td>Dec 2023</td>
</tr>
<tr>
<td>Treatment Resistant Depression</td>
<td>NCT03653858a Controlled Randomized Clinical Trial to Assess Efficacy of Deep Brain Stimulation of the siMFB in Patients With Treatment Resistant Major Depression (FORSEIII)</td>
<td>47</td>
<td>Jun 2023</td>
</tr>
<tr>
<td></td>
<td>NCT01984710 Deep brain stimulation for treatment resistant depression Medtronic Activa PC+S</td>
<td>20</td>
<td>Sep 2023</td>
</tr>
<tr>
<td></td>
<td>NCT00367003 Deep Brain Stimulation for Treatment Resistant Depression</td>
<td>40</td>
<td>Nov 2024</td>
</tr>
<tr>
<td>Unpublished</td>
<td>NCT01801319 A Clinical Evaluation of Subcallosal Cingulate Gyrus Deep Brain Stimulation for Treatment-Resistant Depression</td>
<td>40</td>
<td>Dec 2017 (status unknown)</td>
</tr>
<tr>
<td></td>
<td>NCT01329133 Deep Brain Stimulation and Obsessive-Compulsive Disorder (STOC2)</td>
<td>31</td>
<td>Apr 2019 (completed)</td>
</tr>
<tr>
<td></td>
<td>NCT01973478 Deep Brain Stimulation in Patients With Chronic Treatment Resistant Depression</td>
<td>9 enrolled</td>
<td>Jan 2020 (suspended)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

* Denotes industry-sponsored or cosponsored trial.
# CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. 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.

**CPT**

**Implantation of Electrodes**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>61850</td>
<td>Twist drill or burr hole for implantation of neurostimulator electrodes, cortical</td>
</tr>
<tr>
<td>61863</td>
<td>Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalaric nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; first array</td>
</tr>
<tr>
<td>61864</td>
<td>Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalaric nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; each additional array (List separately in addition to primary procedure)</td>
</tr>
<tr>
<td>61867</td>
<td>Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalaric nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; first array</td>
</tr>
<tr>
<td>61868</td>
<td>Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalaric nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; each additional array (List separately in addition to primary procedure)</td>
</tr>
</tbody>
</table>

**Implantation of Pulse Generator**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>61885</td>
<td>Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array</td>
</tr>
<tr>
<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>
</tr>
</tbody>
</table>

**Electronic Analysis**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>95970</td>
<td>Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact groups[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 reprogramming</td>
</tr>
<tr>
<td>95983</td>
<td>Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group(s), interleaving, amplitude, pulse width, frequency (Hz), on/off cycling, burst, magnet mode, doe lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain</td>
</tr>
</tbody>
</table>
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 (eg, contact group(s), interleaving, amplitude, pulse width, frequency (Hz), on/off cycling, burst, magnet mode, doe 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

---

**HCPCS**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>L8680</td>
<td>Implantable neurostimulator electrode, each</td>
</tr>
<tr>
<td>L8685</td>
<td>Implantable neurostimulator pulse generator, single array, rechargeable, includes extension</td>
</tr>
<tr>
<td>L8686</td>
<td>Implantable neurostimulator pulse generator, single array, nonrechargeable, includes extension</td>
</tr>
<tr>
<td>L8687</td>
<td>Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension</td>
</tr>
<tr>
<td>L8688</td>
<td>Implantable neurostimulator pulse generator, dual array, nonrechargeable, includes extension</td>
</tr>
</tbody>
</table>

---

**ICD-10 Diagnoses (Effective October 1, 2015)**

<table>
<thead>
<tr>
<th>Code</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>G20</td>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>G21.11</td>
<td>Neuroleptic induced parkinsonism</td>
</tr>
<tr>
<td>G21.19</td>
<td>Other drug induced secondary parkinsonism</td>
</tr>
<tr>
<td>G21.2</td>
<td>Secondary parkinsonism due to other external agents</td>
</tr>
<tr>
<td>G21.3</td>
<td>Postencephalitic parkinsonism</td>
</tr>
<tr>
<td>G21.4</td>
<td>Vascular parkinsonism</td>
</tr>
<tr>
<td>G24.1</td>
<td>Genetic torsion dystonia</td>
</tr>
<tr>
<td>G24.2</td>
<td>Idiopathic nonfamilial dystonia</td>
</tr>
<tr>
<td>G24.3</td>
<td>Spasmodic torticollis</td>
</tr>
<tr>
<td>G24.9</td>
<td>Dystonia, unspecified</td>
</tr>
<tr>
<td>G25.0</td>
<td>Essential tremor</td>
</tr>
<tr>
<td>G25.1</td>
<td>Drug-induced tremor</td>
</tr>
<tr>
<td>G25.2</td>
<td>Other specified forms of tremor</td>
</tr>
</tbody>
</table>

---

**REVISIONS**

<table>
<thead>
<tr>
<th>Date</th>
<th>Revision Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>06-13-2011</td>
<td>Updated Description section.</td>
</tr>
<tr>
<td></td>
<td>In the Policy Title section, removed “of the Thalamus” to read “Deep Brain Stimulation.”</td>
</tr>
<tr>
<td></td>
<td>In the Policy Language section:</td>
</tr>
<tr>
<td></td>
<td>• Item III, A, added “,” and tardive dyskinesia” to read “Other movement disorders,</td>
</tr>
<tr>
<td></td>
<td>including but not limited to multiple sclerosis, post-traumatic dyskinesia, and tardive</td>
</tr>
<tr>
<td></td>
<td>dyskinesia.”</td>
</tr>
<tr>
<td></td>
<td>• Item III, C, added “Other psychiatric or neurologic disorder, including but not limited to</td>
</tr>
<tr>
<td></td>
<td>Tourette syndrome,” and , depression, and epilepsy” to read “other psychiatric or</td>
</tr>
<tr>
<td></td>
<td>neurologic disorder, including but not limited to Tourette syndrome, obsessive compulsive</td>
</tr>
<tr>
<td></td>
<td>disorder, depression, and epilepsy.”</td>
</tr>
<tr>
<td></td>
<td>Added Policy Guidelines</td>
</tr>
</tbody>
</table>
## REVISIONS

Updated Rationale section.

In the Coding section:
- Removed CPT codes: 61567, 95971.
- Removed HCPCS codes: L8681, L8682, and L8683.
- Added CPT codes: 95970.
- Deleted Diagnosis code, 333.7. Code requires a 5th digit.
- Added Diagnosis codes: 333.79, 333.89.

Revision section added.

In the Reference section:
- Updated Reference section.
- Added "Other References" section.

09-17-2013

Updated Description section.

In Policy section:
- In Item III, C, added "anorexia nervosa, alcohol addiction, chronic pain," to read "other psychiatric or neurologic disorder, including but not limited to Tourette syndrome, obsessive compulsive disorder, depression, anorexia nervosa, alcohol addiction, chronic pain, and epilepsy."

Updated Rationale section.

In Coding section:
- Added ICD-10 Diagnosis codes *(Effective October 1, 2014)*

Updated Reference section.

02-10-2015

Description section updated

In Policy section:
- Added the medically necessary indication of "Bilateral deep brain stimulation of the thalamus may be considered medically necessary in patients with disabling, medically unresponsive tremor in both limbs due to essential tremor or Parkinson disease."
- In Item III A 2 added "motor portion of the" to read, "a minimal score of 30 points on the motor portion of the Unified Parkinson Disease Rating Scale..."
- In Item III B revised "greater" to "older" to read, "Patients aged older than 7 years with..."
- In Item IV C added "Alzheimer disease" to the experimental / investigational indications to read, "other psychiatric or neurologic disorder, including but not limited to Tourette syndrome, depression, obsessive-compulsive disorder, Alzheimer disease, anorexia nervosa, alcohol addiction, chronic pain, and epilepsy"

Rationale section updated

In Coding section:
- Updated nomenclature in CPT/HCPCS codes: 61864, 61868, 61886, 95970, 95979
- Added Coding instructions

References updated

05-24-2017

Description section updated

In Policy section:
- In Item II added "upper" to read "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."
- In Item III A 3 added "ONE of the following:" and "OR Parkinson disease for at least 4 years" to read "ONE of the following:
  a) a minimal score of 30 points on the motor portion of the Unified Parkinson Disease Rating Scale when the patient has been without medication for approximately 12 hours OR
  b) Parkinson disease for at least 4 years"

Rationale section updated

In Coding section:
**REVISIONS**

<table>
<thead>
<tr>
<th>Date</th>
<th>Revisions</th>
</tr>
</thead>
</table>
| 01-01-2019 | - Updated a coding notation  
             - References updated  
             - Definition section updated  
             - Rationale section updated  
             - In Coding section:  
               - Added CPT Codes: 95976, 95977, 95983, 95984  
               - Removed CPT Codes: 95978, 95979  
               - Revised CPT Code: 95970  
             - References updated |
| 07-01-2019 | - Definition section updated  
             - Rationale section updated  
             - In Coding section:  
               - Removed CPT Codes: 95976, 95977  
             - References updated |
| 08-21-2020 | - Definition section updated  
             - In Policy section:  
               - In Item III A 3 a) revised “minimal” to “minimum” for clarity of the wording. There is no change of intent on the policy.  
             - Rationale section updated  
             - References updated |

**REFERENCES**


Other References
1. Blue Cross and Blue Shield of Kansas Behavioral Health Liaison Committee, June 6, 2006 (see Blue Cross and Blue Shield of Kansas Newsletter, Blue Shield Report. MAC–02-06).
2. Blue Cross and Blue Shield of Kansas Medical Advisory Committee meeting, August 6, 2006 (see Blue Cross and Blue Shield of Kansas Newsletter, Blue Shield Report. MAC–02-06).