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Deep Brain Stimulation

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Coverage

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

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

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

- Those with Parkinson disease and ALL of the following:
  - A good response to levodopa; AND
  - Motor complications not controlled by pharmacologic therapy; AND
  - One of the following:

    - A minimum score of 30 points on the motor portion of the Unified Parkinson Disease Rating Scale (UPDRS) when the patient has been without medication for approximately 12 hours; or
    - Parkinson disease for at least 4 years;
- Individuals older than 7 years with chronic, intractable (drug-refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, or cervical dystonia (torticollis).

Adaptive deep brain stimulation for Parkinson disease **is considered experimental, investigational and/or unproven** (see Policy Guidelines).

Deep brain stimulation for other movement disorders, including but not limited to tardive dyskinesia and post-traumatic dyskinesia, is considered **is considered experimental, investigational and/or unproven**.

Deep brain stimulation for the treatment of chronic cluster headaches **is considered experimental, investigational and/or unproven**.

Deep brain stimulation for the treatment of other psychiatric or neurologic disorders, including but not limited to epilepsy, Tourette syndrome, depression, obsessive-compulsive disorder, anorexia nervosa, alcohol addiction, Alzheimer disease, multiple sclerosis tremor, and chronic pain, **is considered experimental, investigational and/or unproven**.

Policy Guidelines

Disabling, medically unresponsive tremor is defined as all of the following:
- Tremor causing significant limitation in daily activities;
- Inadequate control by maximal dosage of medication for at least 3 months before implant.

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

Parkinson disease is a complex condition and might entail a complex system of care particularly when the disease has advanced. Adaptive DBS (aDBS) is a closed-loop system incorporating feedback from brain signals to dynamically adjust stimulation parameters. It is a more personalized approach to treatment of advanced disease and holds promise for reducing stimulation duration and energy consumption while treating motor related issues such as dyskinesia. The Food and Drug Administration (FDA) submission for aDBS by Medtronic was as an optional programming feature for Parkinson's Disease in existing devices. It was not studied

in bilaterally implanted neurostimulators, and the labeling instructs not to use aDBS with more than one implanted neurostimulator.

Description

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

Background

Deep Brain Stimulation

Deep brain stimulation involves the stereotactic placement of an electrode into the brain (i.e., hypothalamus, thalamus, globus pallidus, or subthalamic nucleus). The electrode is initially attached to a temporary transcutaneous cable for short-term stimulation to validate treatment effectiveness. Several days later, the patient returns for permanent subcutaneous surgical implantation of the cable and a radiofrequency-coupled or battery-powered programmable stimulator. The electrode is typically implanted unilaterally on the side corresponding to the most severe symptoms. However, the use of bilateral stimulation using 2 electrode arrays has also been investigated in patients with bilateral, severe symptoms. After implantation, noninvasive programming of the neurostimulator can be adjusted to the patient's symptoms. This feature may be important for patients with Parkinson disease, 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

NOTE: This section is to be used for informational purposes only. U.S. Food and Drug Administration (FDA) approval alone is not a basis for coverage.

In 1997, the Activa® Tremor Control System (Medtronic) was approved by the FDA through the pre-market approval process for deep brain stimulation. The Activa Tremor Control System consists of an implantable neurostimulator, a deep brain stimulator lead, an extension that connects the lead to the power source, a console programmer, a software cartridge to set electrical parameters for stimulation, and a patient control magnet, which allows the patient to turn the neurostimulator on and off or change between high and low settings.

The 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, the 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 7 years of age or above." In 2018, the deep brain stimulation system received an expanded indication as an adjunctive therapy for epilepsy (P960009-S219). Other deep brain stimulation systems are described in Table 1.

Table 1. Deep Brain Stimulation Systems

System	Manufacturer	FDA Product Code	PMA or HDE	Approval Date	Indications
Activa® Deep Brain Stimulation Therapy System	Medtronic	MBX	P96009	1997	Unilateral or bilateral stimulation of the internal globus pallidus or subthalamic nucleus for symptoms off Parkinson disease or primary dystonia
Reclaim® DBS Therapy for Obsessive Compulsive Disorder	Medtronic	OLM	H050003	2009	Bilateral stimulation of the anterior limb of the internal capsule for severe obsessive-compulsive disorder
Brio Neurostimulation System	St. Jude Medical	NHL	P140009	2015	Parkinsonian tremor (subthalamic nucleus) and essential tremor (thalamus)
Infinity DBS	Abbott Medical/St. Jude Medical	PJS	P140009	2016	Parkinsonian tremor
Vercise DBS System	Boston Scientific	NHL	P150031	2017	Moderate-to-advanced levodopa-responsive PD inadequately controlled with medication alone
Medtronic DBS System for Epilepsy	Medtronic	MBX	P960009-S219	2018	Expanded indication for epilepsy with bilateral stimulation of the anterior nucleus of the thalamus

Percept PC Deep Brain Stimulation	Medtronic	MHY	P960009-S	2020	Records brain signals while delivering therapy for PD or primary dystonia
Vercise Genus DBS System	Boston Scientific	NHL	P150031-S034	2021	Stimulation of the subthalamic nucleus and globus pallidus for PD
SenSight Directional Lead System	Medtronic	MHY	P960009	2021	Unilateral or bilateral stimulation for PD, tremor, dystonia, and epilepsy
BrainSense™ Adaptive Deep Brain Stimulation	Medtronic	MHY	P960009	2025	Automatically adjusted therapeutic stimulation to maximize reduction of PD symptoms

DBS: deep brain stimulation; FDA: U.S. Food and Drug Administration; HDE: humanitarian device exemption; PD: Parkinson disease; PMA: premarket approval.

Rationale

Medical policies 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, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 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. Randomized controlled trials 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, and pharmacologic therapy. 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. 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 following PICO was used to select literature to inform this policy.

Populations

The relevant populations of interest are individuals with essential tremor or tremor in Parkinson disease.

Interventions

The therapy being considered is deep brain stimulation, unilateral or bilateral stimulation of the thalamus.

Comparators

Parkinson disease is usually treated with medications. Permanent neuroablative procedures (e.g., thalamotomy, pallidotomy) 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 (ADL), and quality of life. Key safety outcomes include death, stroke, depression, cognition, infection, and other device and procedure related events. Length of follow-up was up to 5 years.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Unilateral Stimulation of the Thalamus

Schuurman et al. (2008) reported on 5-year follow-up of 68 patients comparing thalamic stimulation with thalamotomy for the treatment of tremor due to Parkinson disease (n=45 patients), essential tremor (n=13 patients), and multiple sclerosis (MS; n=10 patients). (1) Forty-eight (71%) patients were assessed at 5 years: 32 with Parkinson disease, 10 with essential tremor, and 6 with MS. The Frenchay Activities Index, the primary study outcome measure, was used to assess change in functional status; secondary measures included tremor severity, complication frequency, and patient-assessed outcomes. The mean difference (MD) between interventions, as measured on the Frenchay Activities Index, favored thalamic stimulation at all time points: 4.4 (95% confidence interval [CI], 1.1 to 7.7) at 6 months, 3.3 (95% CI, -0.03 to 6.6) at 2 years, and 4.0 (95% CI, 0.3 to 7.7) at 5 years. The procedures had similar efficacy for suppressing tremors. The effect of thalamic stimulation diminished in half of the patients with essential tremor and 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. (2)

Bilateral Stimulation of the Thalamus

Observational Studies

Putzke et al. (2005) reported on a series of 25 patients with essential tremor treated with bilateral deep brain stimulation for the management of midline tremor (head, voice, tongue, trunk). (3) 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 ($p<.01$). For bilateral stimulation at months 3 and 12, outcome measures were significantly better than unilateral stimulation at month 3 ($p<.05$). Limited sample size precludes interpretation 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 2 reported disequilibria 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 tremor; of these patients, 18 had unilateral and 8 had bilateral implantation. (4) 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 ($p=.02$) and 36% improvement in ADL scores. Patients with unilateral stimulation improved by 46% on motor tremor scores and 51% on ADL

scores (p<.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.

Jost et al. (2023) investigated the long-term effects of bilateral deep brain stimulation of the subthalamic nucleus on quality of life, motor function, and medication requirements in patients with advanced Parkinson's disease. (5) The final analysis included 108 patients, with 62 receiving deep brain stimulation and 46 receiving medication, matched to a subcohort of 25 patients per group. At the 5-year follow-up, the Parkinson's Disease Questionnaire 8 (PDQ-8) and ADL scores worsened only in the medication group (PDQ-8 change: -10.9; 95% CI, -19.0 to -2.7; p=.01; ADL change: -2.0; 95% CI, -3.1 to -0.8; p=.002), while remaining stable in the deep brain stimulation group (PDQ-8 change: -4.3; 95% CI, -13.2 to 4.7; p=.34; ADL change: -0.8; 95% CI, -2.5 to 1.0; p=.38). Furthermore, the group that received deep brain stimulation also experienced favorable effects on motor complications (median difference in change scores between deep brain stimulation and medication: -2.0; 95% CI, -4.0 to -1.0; p<.001) and mobility (-1.0; 95% CI, -2.0 to 0; p=.03).

Directional Deep Brain Stimulation

Randomized Controlled Trial

Three new deep brain stimulation systems with directional leads are currently available (approved by the U.S. Food and Drug Administration [FDA] in 2016, 2017, and 2021). Directional leads potentially enable clinicians to target more specific areas of the brain to be treated with the direct current. Schnitzler et al. (2022) conducted a prospective crossover study with randomized, double-blind endpoint evaluation in 234 patients with Parkinson disease. (6) All patients received conventional deep brain stimulation for 3 months followed by directional deep brain stimulation for 3 months. The therapeutic window was wider after using directional stimulation in 90.6% of patients, with a mean increase of 41% compared to conventional deep brain stimulation.

Section Summary: Essential Tremor and Tremor in Parkinson Disease

Early studies determined 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 have supported these conclusions 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

Clinical Context and Therapy Purpose

The purpose of deep brain stimulation is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with symptoms 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.

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

Populations
The relevant populations of interest are individuals with symptoms associated with Parkinson disease.

Interventions
The therapy being considered is deep brain stimulation of the internal segment of the globus pallidus interna and subthalamic nucleus.

Comparators
The following practice is currently being used to treat Parkinson disease: pharmacologic therapy and physical and speech therapy.

Outcomes
Key efficacy outcomes include motor scores, mobility, disability, ADL, and quality of life. Key safety outcomes include death, stroke, depression, cognition, infection, and other device and procedure related events. Length of follow-up was up to 4 years.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Advanced Parkinson Disease
Systematic Reviews
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. (7) Six RCTs (N=1184) 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 MD, 15.20; 95% CI, 12.23 to 18.18; standard MD, 1.35). In the on-medication phase, there was

also significantly greater motor function with deep brain stimulation than with control (weighted MD, 4.36; 95% CI, 2.80 to 5.92; standard MD, 0.53). Meta-analyses of other outcomes (e.g., 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. (8) 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 relationship 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%. (9) 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.

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

Randomized Controlled Trial

Schuepbach et al. (2013) published an RCT evaluating deep brain stimulation in patients with Parkinson disease and early motor complications. (10) 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 2 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=.002). There were also significant between-group differences in major secondary outcomes, favoring the deep brain stimulation plus medical therapy group (p<.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

Systematic Reviews

A number of meta-analyses have compared the efficacy of globus pallidus interna with subthalamic nucleus stimulation in Parkinson disease patients. (11-17) 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. (13) 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 1 of the following outcome measures: Unified Parkinson's Disease Rating Scale-III, Beck Depression Inventory-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-simulation state (5 studies; MD, -1.39; 95% CI, -3.70 to 0.92) or the on-medication/on-stimulation state (5 studies; MD, -0.37; 95% CI, -2.48 to 1.73). At the 12- and 24-month follow-ups, only 1 to 3 studies reported data on the 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 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 1 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. Studies evaluating deep brain stimulation of the globus pallidus interna or subthalamic nucleus have consistently demonstrated clinically significant improvements in outcomes (e.g., 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 (e.g., 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 1 type of stimulation was clearly superior to the other.

Adaptive Deep Brain Stimulation for Parkinson Disease

Clinical Context and Therapy Purpose

The purpose of adaptive deep brain stimulation is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with symptoms associated with Parkinson disease. Adaptive deep brain stimulation is an optional programming feature for Parkinson disease in existing devices within the Medtronic deep brain stimulation system.

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

Populations

The relevant populations of interest are individuals with symptoms associated with Parkinson disease.

Interventions

The therapy being considered is deep brain stimulation of the internal segment of the globus pallidus interna and subthalamic nucleus.

Comparators

The following practice is currently being used to treat Parkinson disease: continuous deep brain stimulation.

Outcomes

Key efficacy outcomes include motor scores, mobility, disability, ADL, and quality of life. Key safety outcomes include stimulation-related adverse events, and other device and procedure-related events.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials

The ADAPT-PD clinical trial by Stanslaski et al. (2024) is a multicenter randomized crossover study evaluating the feasibility and efficacy of adaptive deep brain stimulation (aDBS) for Parkinson disease using the Medtronic Percept™ PC neurostimulator. (18, 19) The primary

cohort enrolled 68 patients who were implanted with subthalamic nucleus or globus pallidus internus deep brain stimulation leads configured to ring mode monopolar or dual monopolar stimulation, assessing local field potential (LFP) signal detection and aDBS programming. Two algorithms (single and dual threshold modes) were tested, adjusting stimulation amplitude based on real-time LFP fluctuations. There were also 17 patients enrolled for a directional stimulation cohort, where patients were configured to directional monopolar or dual monopolar stimulation. Patients first underwent continuous deep brain stimulation followed by the aDBS adjustment phase. In the aDBS evaluation phase, they were randomized to 30 days of either single or dual threshold, then switched to the other mode for another 30 days if tolerated.

The primary efficacy endpoint for each aDBS mode was a binary success/failure outcome from a comparison of the patient's “On” time without troublesome dyskinesia during the continuous deep brain (cDBS) stimulation baseline phase and the aDBS evaluation phase applicable to that specific mode. The outcome was captured from patient report using Parkinson’s Disease Home Diary, with success defined as cDBS Baseline average “On” time without troublesome dyskinesia minus 2 hours per day. (19) Primary safety endpoints included stimulation-related adverse events, serious adverse events, adverse events, and device deficiencies. Of the 85 patients enrolled in the study, 60 patients completed the aDBS evaluation phase. Fifty-four patients completed the long-term follow-up phase. After accounting for exclusions and discontinuations, the total full analysis set (FAS) was comprised of 45 patients.

In the single-threshold and dual-threshold FAS groups, 85.7% (30/35) and 95% (38/40) of patients, respectively, completed Parkinson's Disease home diaries. (19) The success rate for single-threshold aDBS was 78.9%, with a 97.5% lower confidence limit of 59.4%, while dual-threshold aDBS had a 91% success rate with a 97.5% lower confidence limit of 75.6%. A sensitivity analysis for the primary outcome was also conducted, which included complete case (CC), as-treated (AT), primary cohort modified intention-to-treat (PC mITT), and the directional stimulation cohort (CC+DSCC). In the CC, AT, and CC+DSCC analysis sets, the 97.5% confidence interval lower bounds for the primary success rate were at least 67.2% for single-threshold aDBS and 76.0% for dual-threshold aDBS. In the single- and dual-threshold PC mITT sets, which included all FAS subjects and those who initially set up but later found aDBS unacceptable, the lower bounds were 46.0% and 62.6%, respectively.

Safety outcomes were based on the full cohort of 85 patients. (19) Overall, 78.8% of subjects experienced adverse events, with 56.5% of patients experiencing adverse events related to the device. Serious adverse events occurred in 17.6% of subjects, including one participant who had 2 serious device-related events (a fall and a spinal fracture) during the extended access phase.

Bronte-Stewart et al. (2025) reported on the long-term outcomes of the ADAPT-PD pivotal trial, a prospective, international, open-label, nonrandomized clinical trial evaluating adaptive deep brain stimulation (aDBS) in patients with Parkinson disease who were previously stable receiving continuous deep brain stimulation (cDBS). (20) Participants were enrolled from December 2020 to July 2022 across sites in the United States, Canada, and Europe. Eligible

participants were assessed while receiving stable cDBS, and those who tolerated 2 aDBS modes were randomized and blinded to 30 days in each mode (single-blind crossover design) using the Medtronic Percept™ PC neurostimulator; those who tolerated only 1 mode were assessed in that mode only. The 2 aDBS modes evaluated were single-threshold (ST-aDBS) and dual-threshold (DT-aDBS), both of which adjust stimulation amplitude in response to real-time fluctuations in the subthalamic beta local field potential (LFP). The primary endpoint required that at least 50% of participants achieve a performance goal of on-time without troublesome dyskinesia, no less than 1 standard deviation below the continuous deep brain stimulation baseline average. Of the 68 participants enrolled, the full analysis set comprised 45 patients. The primary endpoint was met for both aDBS modes: the success rate was 78.9% (97.5% lower confidence limit 59.4%) for ST-aDBS and 91.0% (97.5% lower confidence limit 75.6%) for DT-aDBS. Forty participants completed a long-term follow-up of approximately 10 months, during which aDBS continued to demonstrate tolerability and safety. Serious adverse events were reported in 17.6% of subjects, including 1 participant who experienced 2 severe device-related injuries during the extended access phase.

Section Summary: Adaptive Deep Brain Stimulation for Parkinson Disease

One randomized trial assessed the feasibility and efficacy of adaptive deep brain stimulation for control of Parkinson disease symptoms. The primary efficacy outcome measured the change in "On" time without troublesome dyskinesia, with success rates of 78.9% for single-threshold aDBS and 91% for dual-threshold aDBS. Extended follow-up demonstrated sustained benefits with dual-threshold aDBS showing additional improvements. Safety analysis showed that overall, 78.8% of patients experienced adverse events, 56.5% had device-related events, and 17.6% had serious adverse events, including one participant with 2 severe device-related injuries.

Primary 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. (21) 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 purpose of deep brain stimulation is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with primary dystonia.

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

Populations
The relevant population of interest is individuals with primary dystonia. Primary dystonia is defined when dystonia is the only symptom unassociated with other pathology.

Interventions
The therapy being considered is deep brain stimulation of the globus pallidus interna or subthalamic nucleus.

Comparators
The following practice is currently being used to treat primary dystonia: pharmacologic therapy or permanent neuroablative procedures (e.g., thalamotomy, pallidotomy). Treatment options for dystonia include oral or injectable medications (i.e., botulinum toxin) and destructive surgical or neurosurgical interventions (i.e., thalamotomies or pallidotomies) when conservative therapies fail.

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

Outcomes
Key efficacy outcomes include clinical severity of dystonia and disability, 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.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Primary Dystonia

Systematic Reviews

Moro et al. (2017) published a systematic review of literature published through November 2015 on primary dystonia (also known as isolated dystonia). (22) Reviewers included studies with at least 10 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. (23)

Randomized Controlled Trials

The 2 RCTs identified in the systematic reviews are described in Tables 2 through 5. Kupsch et al. (2006) randomized 40 patients with primary segmental or generalized dystonia to deep brain stimulation or sham stimulation for 3 months. (24) 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 6 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. (25) 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 Craniocervical Dystonia Questionnaire-24 score. During the 3-month blinded study period, 22 adverse events were reported in 20 (63%) patients in the neurostimulation group, and 13 adverse events were reported in 12 (40%) patients in the sham group. Of these 35 adverse events, 11 (31%) were serious. Additionally, 40 adverse events, 5 of which were serious, occurred during 9 months of the open-label extension period. During the study, 7 patients experienced dysarthria (i.e., slightly slurred speech), which was not reversible in 6 patients.

Wang et al. (2025) published a multicenter, randomized, double-blind, controlled trial evaluating subthalamic nucleus deep brain stimulation in patients with idiopathic isolated generalized or segmental dystonia. (26) The trial enrolled 67 patients ages 6 to 60 years at 7 hospitals in China and randomized patients to undergo implantation targeting either the globus pallidus interna or subthalamic nucleus. Following implantation, patients within each target group were further randomized to active stimulation or sham stimulation for 3 months. The primary outcome was the change in the Burke-Fahn-Marsden Dystonia Rating Scale movement score. In the subthalamic nucleus group, patients assigned to active stimulation had significantly greater improvement at 3 months than those assigned to sham stimulation. Improvement in motor scores with subthalamic nucleus stimulation was maintained at open-label follow-up at 6 months and 3 years. No ongoing serious adverse events were reported.

Table 2. Characteristics of Randomized Controlled Trials of Deep Brain Stimulation for Primary Dystonia

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	***Comparator***
Wang et al. (2025) (26)	China	7	2018 to 2019	Patients ages 6 to 60 years with genetic or idiopathic isolated generalized or segmental dystonia and an unsatisfactory response to optimal pharmacologic treatment	n=35 17 STN, 18 GPi	n=32 Sham stimulation; 13 STN, 19 GPi
Kupsch et al. (2006) (24); NCT00142259	Germany, Norway, Austria	10	2002 to 2004	Patients ages 14 to 75 years with marked disability owing to primary generalized or segmental dystonia despite optimal pharmacologic	n=20 GPi DBS	n=20 Sham

				treatment with disease duration of at least 5 years.		
Volkmann et al. (2014) (25); NCT00148889	Germany, Norway, Austria	10	2006 to 2008	Adults under the 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.	n=32 GPi DBS	n=30 Sham

DBS: deep brain stimulation; GPi: globuspallidusinternus; STN: subthalamic nucleus; TWSTRS: Toronto Western Spasmodic Torticollis Rating Scale.

Table 3. Results of Randomized Controlled Trials of Deep Brain Stimulation for Primary Dystonia

Study	**Dystonia Severity**	**Disability**	**Quality of Life**	**Depression Symptoms**	**Serious Adverse Events**
Wang et al. (2025) (26)	**Change in BFMDRS movement at 3 months, Mean (SD)**		**Change in SF-36 at 3 months, Mean (SD)**	**Change in BDI at 3 months, Mean (SD)**	
N	66		66	66	67
DBS	STN -17.76 (16.03) GPi -16.90 (16.01)		STN PCS-15.94 (26.41) STN MCS-14.25 (12.39) GPi PCS-15.56 (29.45) GPi MCS-12.22 (20.33)	STN-3.35 (4.91) GPi-2.83 (7.42)	2 serious adverse events: 1 subcutaneous infection and 1 cerebrospinal fluid leakage; both resolved after treatment. No ongoing serious
Sham	STN -6.12 (8.97) GPi -1.50 (8.51)		STN PCS-2.69 (18.44) STN MCS-6.46	STN-0.62 (6.78) GPi-1.11 (3.87)	

			(19.90) GPi PCS-0.0 (27.64) GPi MCS-5.47 (23.56)		adverse events and no device-related adverse events were reported.
Treatment effect (95% CI)	STN MD=11.64 (1.12 to 22.16); p=.028 GPi MD=15.40 (6.66 to 24.14); p <.001		STN PCS MD= 13.25 (-31.03 to 4.53) STN MCS MD= 7.79 (-20.17 to 4.60) GPi PCS MD= 15.56 (-34.61 to 3.50); p=.148 GPi MCS MD= 6.75 (-21.47 to 7.97); p=.358	STN MD=2.74 (-1.63 to 7.10); p=.120 GPi MD=1.73 (-2.19 to 5.65); p=.377	
Kupsch et al. (2006) (24)	**Change in BFMDRS movement at 3 months, Mean (SD)**	**Change in BFMDRS disability at 3 months, Mean (SD)**	**Change in SF-36 at 3 months, Mean (SD)**	**Change in BDI at 3 months**	
N	40	39	33	30	
DBS	-15.8 (14.1)	3.9 (2.9)	PCS: 10.1 (7.4) MCS: 5.2 (15.0)	-5.1 (8.4)	3 (8%); 3 related to lead dislodgement or 1 related to infection requiring hospitalization
Sham	-1.4 (3.8)	0.8 (1.2)	PCS: 3.8 (8.4) MCS: 0.2 (8.7)	-0.5 (10.2)	
Treatment effect (95% CI)	MD=14.40 (8.0 to 20.80); p<0.01	MD=3.10 (1.72 to 4.48)	PCS MD=6.30 (1.06 to 11.54) MCS MD=5.00 (-2.14 to 12.14)	MD=4.60 (-2.06 to 11.26)	

Volkmann et al. (2014) (25)	Change in TWSTRS severity at 3 months	Change in TWSTRS disability at 3 months	Change in SF-36 at 3 months	Change in BDI at 3 months	
N	62	61	57	61	
DBS	-5.1 (5.1)	-5.6 (5.6)	PCS: 6.6 (21.9) MCS: 11.3 (18.2)	-3.5 (5.6)	16 (26%); 11 related to surgery or device, 1 related to medication or stimulation, 4 related to dystonia
Sham	-1.3 (2.4)	-1.8 (3.8)	PCS: 3.6 (19.2) MCS: 8.9 (14.4)	-0.4 (3.7)	
Treatment effect (95% CI)	MD=3.80 (1.84 to 5.76); p<0.01	MD=3.80 (1.41 to 6.19)	PCS MD=3.00 (-7.71 to 13.71) MCS MD=2.40 (-6.20 to 11.00)	MD=3.10 (0.73 to 5.47)	

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

Table 4. Study Relevance Limitations: Randomized Controlled Trials of Deep Brain Stimulation for Primary Dystonia

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Wang et al. (2025) (26)					1. Only 3 months of double-blind study
Kupsch et al. (2006) (24)					1. Only 3 months of double-blind study
Volkmann et al. (2014) (25)					1. Only 3 months of double-blind study

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

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population

not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 5. Study Design and Conduct Limitations: Randomized Controlled Trials of Deep Brain Stimulation for Primary Dystonia

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Complete-ness[d]	Power[e]	Statistical[f]
Wang et al. (2025) (26)						
Kupsch et al. (2006) (24)			1. Registered after enrollment was complete			
Volkmann et al. (2014) (25)		1, 3. Treating physicians not blinded. Primary outcome assessors blinded but secondary outcomes subject to bias				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[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.

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 case series and 3 RCTs. Overall, 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

Clinical Context and Therapy Purpose

The purpose of deep brain stimulation is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with tardive dyskinesia and tardive dystonia.

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

Populations

The relevant population of interest is individuals with tardive dyskinesia and tardive dystonia.

Interventions

The therapy being considered is deep brain stimulation.

Comparators

The following practice is currently being used to treat tardive dyskinesia and tardive dystonia: pharmacologic therapy.

Outcomes

The general outcomes of interest are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Follow-up in studies has been up to 4 years.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials

One RCT evaluated the efficacy 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 versus sham deep brain stimulation. (27) Twenty-five patients were randomized. In the intention-to-treat analyses, the between group difference of dystonia severity was not significant at 3 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 Randomized Controlled Trials of Deep Brain Stimulation for Tardive Dyskinesia and Tardive Dystonia

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	***Comparator***
Gruber et al. (2018) (27) NCT00331669	Germany	15	2006 to 2009	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	n=12 Pallidal DBS	n=13 Sham

DBS: deep brain stimulation.

Table 7. Results of Randomized Controlled Trials of Deep Brain Stimulation for Tardive Dyskinesia and Tardive Dystonia

Study	Dystonia Severity	Disability	Quality of Life	Depression Symptoms	Serious Adverse Events
Gruber et al. (2018) (27)	Change in BFMDRS Movement score at 3 months, Mean (SD)	Change in BFMDRS Disability score at 3 months, Mean (SD)	Change in SF-36 at 3 months, Mean (SD)	HAM-D at 3 months, Mean (SD)	
N	25	25	24	24	
DBS	-5.6 (9.1)	0.5 (5.5)	PCS: 5.4 (10.0)	1.4 (5.5)	3 events (episodes of

			MCS: 0.5 (10.9)		confusion, worsening of dystonia following gastrointestinal infection, skin erosion)
Sham	-5.9 (13.9)	-0.3 (1.2)	PCS: 1.6 (7.8) MCS: -0.6 (4.8)	2.2 (6.6)	
Treatment effect (95% CI)	p=0.72	p=0.43	PCS: p=0.17 MCS: p=0.53	p=0.69	

BFMDRS: Burke-Fahn-Marsden-Dystonia-Rating-Scale; CI: confidence interval; DBS: deep brain stimulation; HAM-D: Hamilton Depression Score; MCS: Mental component score; PCS: Physical Component Score; SD: standard deviation; SF-36: short form 36 item quality of life survey.

Table 8. Study Relevance Limitations: Randomized Controlled Trials of Deep Brain Stimulation for Tardive Dyskinesia and Tardive Dystonia

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-up[e]
Gruber et al. (2018) (27)					1. 3-month follow-up in blinded period

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

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such; 5. Other.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

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

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Gruber et al. (2018) (27)				1. Study powered to include 48 patients but only 25 patients enrolled		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[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
Stimulation of the globus pallidus interna was examined as a treatment for tardive dyskinesia in a multicenter observational study by Damier et al. (2007), with a double-blind evaluation at 6 months (comparison of symptoms in the on and off positions). (28) The trial was stopped early due to successful treatment (>40% improvement at 6 months) in the first 10 patients. In the double-blind evaluation of these patients, stimulation was associated with a mean decrease of 50% in the symptom score when the device was on versus off.

Pouclet-Courtemanche et al. (2016) reported on a case series of 19 patients with severe pharmaco-resistant tardive dyskinesia treated with deep brain stimulation. (29) Patients were assessed 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% to 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 4 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.

Drug-Refractory Epilepsy
Clinical Context and Therapy Purpose
The purpose of deep brain stimulation is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with drug-refractory epilepsy. Approximately one-third of individuals with epilepsy do not respond to anti-epileptic drugs and

are considered to have drug-resistant epilepsy. Individuals 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 following PICO was used to select literature to inform this policy.

Populations
The relevant population(s) of interest are individuals 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 2 tolerated, appropriately chosen and administered anti-epileptic drugs, used as monotherapy or in combination, to achieve seizure freedom. (30) Individuals who are not candidates for resective surgery include those with 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 following practice is currently being used to treat drug-refractory epilepsy: pharmacologic therapy and vagus nerve stimulation. The pharmacologic 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. (31)

Key safety outcomes include death, stroke, depression, cognition, infection and other device and procedure related events. Length of follow-up was up to 7 years.

<u>Study Selection Criteria</u>
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.

- In the absence of such trials, compartive observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Dhaliwal et al. (2025) published a meta-analysis evaluating the efficacy of thalamic deep brain stimulation for drug-resistant epilepsy. (32) A search identified 49 studies encompassing 1,125 patients; targets included the anterior nucleus of the thalamus (41 studies, 981 patients), centromedian nucleus (12 studies, 135 patients), and pulvinar nucleus (2 studies, 9 patients). The most common epilepsy type was focal epilepsy (85.7% for anterior nucleus of the thalamus, 41.5% for centromedian nucleus), with a mean epilepsy duration of approximately 20.9 years. The mean seizure reduction across all thalamic targets was 62.3% (95% CI, 56 to 68.6; p<.01; I^2=80%), with reductions of 64.3% (95% CI, 57.6 to 71.0; I^2=80%) for the anterior nucleus of the thalamus and 69.1% (95% CI, 58.1 to 80.1; I^2=79%) for the centromedian nucleus. Responder rates (defined as ≥50% seizure reduction) were 61.5% (95% CI, 54.1 to 68.9; I^2=82.2%) for the anterior nucleus of the thalamus and 69.09% (95% CI, 54.0 to 84.1; I^2=74.9%) for the centromedian nucleus; seizure freedom rates were low for both targets (anterior nucleus of the thalamus, 3.57% [95% CI, 1.9 to 5.3; I^2=7.2%]; centromedian nucleus, 2.8% [95% CI, 1.4 to 4.2; I^2=0%]). Subgroup analysis by follow-up duration demonstrated improved responder rates for the anterior nucleus of the thalamus at greater than 24 months (67.6%; 95% CI, 61.0 to 74.2) compared with less than 24 months (44.1%; 95% CI, 26.7 to 61.4; test for subgroup differences, p=.01). Risk of bias was assessed using the ROBINS-I tool; most included studies had moderate risk of bias, and the majority were nonrandomized and uncontrolled. Funnel plot analysis showed no strong evidence of publication bias. The authors concluded that further research is required to optimize patient selection, predict individual response, and assess non-seizure-related outcomes, including quality of life.

Randomized Controlled Trials

Trials including 15 patients or more are described in more detail in this section. Study characteristics are in Table 10 and results are in Tables 11a/11b. 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). (33) 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=.002; see Tables 11a/11b). 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, QOLIE-31 scores, but data were not shown. Data for these outcomes are available in the FDA Summary of Safety and Effectiveness, see Tables 11a/11b. (34)

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 10). (35) 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=.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 (7 in the active group, 1 in the control group; p=.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 10). (36) 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 Tables 11a/11b.

Dalic et al. (2022) conducted a single center, double-blind, randomized trial to evaluate the efficacy and safety of DBS targeting the centromedian thalamic nucleus for Lennox-Gastaut Syndrome. (37) The study included 19 randomized patients with severe drug-resistant epilepsy. After completing the pre- and post-implantation phases, half of the participants underwent 3 months of stimulation during the blinded phase, followed by all participants receiving stimulation for an additional 3 months in the unblinded phase. The primary outcome assessed was the percentage of participants achieving at least a 50% reduction in diary-recorded seizures, comparing those who received stimulation to those in the control group at the end of the blinded phase. At the end of the 3-month blinded phase, 50% of the stimulation group achieved at least a 50% reduction in diary-recorded seizures compared to 22% of controls (OR, 3.1; 95% CI, 0.44 to 21.45; p=.25). A significant reduction was observed in electrographic seizures, with 89% of the stimulation group achieving a ≥50% reduction, compared to none in the control group (OR, 23.25; 95% CI, 1.0 to 538.4; p=.05).

Table 10. Summary of Randomized Controlled Trials Characteristics for Epilepsy

Study	Country	Sites	Dates	Participants	Interventions	
					Active	***Comparator***
Fisher et al. (2010) (33) Troster et al. (2017) (35) SANTE	United States	17	NR	Patients with partial seizures, including secondary generalized seizures, refractory to ≥ 3 medications	5-V stimulus intensity (n=54)	No stimulation (n=55)
Cukiert et al. (2017) (36)	Brazil	1	2014-2016	Patients with temporal lobe epilepsy refractory to ≥ 3 medications	Weekly 0.4-V to 2-V stimulus intensity (n=8)	Weekly impedance testing, no stimulation (n=8)
Dalic et al. (2022); (37) ESTEL	Australia	1	2017 to 2019	Patients with LGS with ≥4 seizures per month who previously failed ≥3 medications	Immediate stimulation (i.e., starting 3 months after implantation) (n=10)	Delayed stimulation/control (i.e., starting 6 months after implantation) (n=9)

LGS: Lennox-Gastaut Syndrome; NR: not reported; SANTE: Stimulation of the Anterior Nuclei of the Thalamus for Epilepsy; V: volts.

Table 11a. Summary of Randomized Controlled Trials Outcomes for Epilepsy

Study	Seizure Reduction, % (p)			Responder (50% or more reduction in seizure frequency)	Hospitalizations
	1-mo	2-mo	3-mo		Mean (SD) annual hospitalizations per patient.
Fisher et al. (2010) (33); Troster et al. (2017) (35); SANTE					
DBS				30%[a]	0.08 (0.56)[a]
Sham				26%[a]	0.37 (1.17)[a]
Between Group Difference	-11% (NS)	-11% (NS)	-29% (0.002)	p=0.83[a]	p=0.11[a]
	FIAS at 6 Months				
Cukiert et al. (2017) (36)					

Stimulation On	4 seizure-free; 3 responders; 1 no response		
Stimulation Off	0 seizure-free; 3 responders; 5 no response		
Dalic et al. (2022) (37)			
DBS		50%	
Control		22%	
		OR, 3.1; 95% CI, 0.44 to 21.45; p=.25	

CI: confidence interval; DBS: deep brain stimulation; FIAS: focal impaired awareness seizure; mo: months; NS: not statistically significant; OR: odds ratio; SANTE: Stimulation of the Anterior Nuclei of the Thalamus for Epilepsy; SD: standard deviation.

[a] Not reported in publication but reported in FDA Summary of Safety and Effectiveness.

Table 11b. Summary of Randomized Controlled Trials Outcomes for Epilepsy Continued

Study	Rescue Medications (at least one use)	Seizure Severity	Quality of Life	Adverse Events
		Change (SD) in LSSS	Change (SD) in QOLIE-31	
Fisher et al. (2010) (33); Troster et al. (2017) (35); SANTE				
DBS	22%[a]	-8.2 (17.8)[a]	2.5 (8.7)[a]	
Sham	22%[a]	-6.8 (19.6) [a]	2.8 (8.0)[a]	
Between Group Difference	p=0.87[a]	p=0.70[a]	p=0.55[a]	3 months: higher rate of depression and memory adverse events in treatment group (difference disappeared in long-term follow-up)
Cukiert et al. (2017) (36)				
Stimulation On				2 patients with local skin erosions at cranial site of implant, treated with antibiotics
Stimulation Off				
Dalic et al. (2022) (37)				
DBS				
Control				

DBS: deep brain stimulation; LSSS: Liverpool Seizure Severity Scale; NS: not statistically significant; QOLIE-31: Quality of Life in Epilepsy Score; SANTE: Stimulation of the Anterior Nuclei of the Thalamus for Epilepsy; SD: standard deviation.

[a] Not reported in publication but reported in FDA Summary of Safety and Effectiveness.

Study limitations are described in Tables 12 and 13. The SANTE study included relevant patients and outcomes and had few design and conduct limitations. Both publications did not report several important outcomes such as quality of life and functional outcomes, 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. (36)

Table 12. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-up[e]
Fisher et al. (2010) (33) SANTE				1. Responder and freedom from seizure, quality of life outcomes not reported in publication; reported in SSED	
Cukiert et al. (2017) (36)				1. Quality of life and functional outcomes not reported	
Dalic et al. (2022) (37)				1. Quality of life and functional outcomes not reported 7. Limitation of diary-based assessments of seizure frequency	

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

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

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5. Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 13. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Fisher et al. (2010) (33) SANTE			2. Several seizure outcomes as well as quality of life collected but not reported in publication; available in SSED			
Cukiert et al. (2017) (36)				2. No mention of how missing diary data or other missing data were handled in analysis. No flow of participants described	1. No power calcula-tions	2. Not clear if analyses were done independently for each time point or if analyses adjusted for multiple observations 4. Comparative treatment effects not calculated
Dalic et al. (2022) (37)		1. Both blinded and				

		unblinded phases				

SANTE: Stimulation of the Anterior Nuclei of the Thalamus for Epilepsy; SSED: Summary of Safety and Effectiveness.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[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). (38) 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 ($p<.001$ for both). During the trial, 39 (35%) of 110 patients had a device-related serious adverse event, most of which occurred in the first months after implantation. They included implant-site infection (10% of patients) and lead(s) not within target (8.2% of patients). Seven deaths occurred during the trial, and none were 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). (34) 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). At year 7, QOLIE-31 scores (n=67) improved by a mean of 4.9 (SD, 11) points. 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 SANTE[a]

Outcomes	Median seizure frequency (change from BL)	Responder (≥50% reduction in seizure frequency)	LSSS, Mean (SD)	QOLIE-31, ≥ 5-point improvement	Hospitalizations, mean (SD) annual number of hospitalizations per patients	Serious device-related adverse event
N	50	50	67	67	80	110
Estimate	-75%[b]	74%	-18.1 (23.5)	43%	0.08 (0.28)	34.5%

BL: baseline; LSSS: Liverpool Seizure Severity Scale; QOLIE-31: Quality of Life in Epilepsy Score; SD: standard deviation; 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. (39) 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. The mean follow-up was 6.3 years. Median seizure reduction from baseline was 71% at year 1, 74% at year 2, and ranged from 62% to 80% through 11 years of follow-up. Complications included 1 symptomatic intracranial hemorrhage, 1 infection requiring removal and reimplantation, and 2 lead disconnections.

Peltola et al. (2023) reported data from the Medtronic Registry for Epilepsy (MORE), a study aiming to understand the safety and longer-term effectiveness of deep brain stimulation of the anterior nucleus of the thalamus. (40) This study includes 170 adults with drug-resistant epilepsy from 25 centers in 13 countries. Most patients (94%) received the Activia stimulator. The authors do not report how many patients were not candidates for resective surgery but did report that 24 patients (20%) had at least 1 resective epilepsy procedure before undergoing deep brain stimulation. At the 2-year follow-up, there was a 43.4% change from baseline in the median monthly seizure frequency (15.8 at baseline to 8.8; p<.0001). In a subgroup of patients who completed 5 years of follow-up (n=47), the median monthly seizure frequency decreased by 55.1% (16 at baseline to 7.9; p<.0001).

Yan et al. (2023) reported on an observational study that included 65 patients with refractory epilepsy who were not eligible for resection. (41) Patients in this trial received deep brain stimulation of the anterior nucleus of the thalamus (n=45), subthalamic nucleus (n=16), centromedian nucleus (n=3), or pulvinar nucleus (n=1). Of the total 65 patients, 45 (70.8%) were deemed responders (average decrease in seizure frequency, 81.2%; range, 51.6% to

100%), but longer-term follow-up was only available for patients who received deep brain stimulation of the anterior nucleus of the thalamus or subthalamic nucleus. Among patients who underwent deep brain stimulation of the anterior nucleus of the thalamus, 29 out of 46 (64.4%) responded to treatment, and 4 (8.9%) reported being seizure-free at 1 year. Among patients who underwent deep brain stimulation of the subthalamic nucleus, 13 out of 16 (81%) responded to treatment, and 2 (13%) reported being seizure-free at 6 months.

Section Summary: Drug-Refractory Epilepsy

A meta-analysis of 49 studies (1,125 patients) evaluating thalamic deep brain stimulation reported mean seizure reductions of approximately 62% to 69% across anterior nucleus of the thalamus and centromedian nucleus targets, with responder rates of approximately 62% to 69%; seizure freedom rates were low for both targets. The majority of included studies were nonrandomized and uncontrolled, and there was substantial heterogeneity across studies. The largest RCT (N=110) 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 QOLIE-31 scores. In the uncontrolled follow-up period of the RCT and in multiple observational studies, patients reported fewer seizures compared with baseline; however, without a control group, interpretation of results is limited. An additional 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

The purpose of deep brain stimulation is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with Tourette syndrome. 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 following PICO was used to select literature to inform this policy.

Populations

The population of interest is individuals 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, substantia periventricularis, and nucleus ventro-oralisinternus, subthalamic nucleus, caudate nucleus, globus pallidus interna, and the anterior limb of the internal capsule and nucleus accumbens.

Comparators
The following practice is currently being used to treat Tourette syndrome: pharmacologic therapy and cognitive-behavioral therapy. Intervention may be initiated when symptoms of Tourette syndrome are disabling or cause difficulty in functioning. Individuals may require a therapy to treat tics, as well as comorbid attention deficit hyperactivity disorder or OCD. Medication treatment for tics might include antidopaminergic drugs, alpha adrenergic agonists drugs, topiramate, or injections of botulinum toxin. Behavioral therapy, primarily based on habit reversal therapy is also used.

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

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

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews
Several systematic reviews of the literature on deep brain stimulation for Tourette syndrome have been published. (42-48) Most recent systematic reviews are qualitatively described in the literature.

Baldermann et al. (2016) conducted pooled analyses of study data. (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, 1 used bilateral globus pallidus stimulation, and 1 used both. The primary outcome was the YGTSS. In a pooled analysis of within-subject pre-post data, there was a median improvement of 53% in YGTSS score, a decline from a median score of 83 to 35 at last follow-up. Moreover, 81% of patients showed at least a 25% reduction in YGTSS score and 54% showed improvements of 50% or more. In addition, data were pooled from the 4 crossover RCTs: 27 patients received 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 MD, 0.96; 95% CI, 0.36 to 1.56). Reviewers noted that the effect size of 0.96 would be considered large.

Wehmeyer et al. (2021) also conducted a pooled analysis. (47) A total of 65 studies with 376 patients were included; the primary outcome was YGTSS scores and scores were significantly reduced at maximum follow-up of median 25 months (p<.001). The median scores decreased from 79.92 points (interquartile range [IQR], 13.25) to 34.69 points (IQR, 20.93) post-surgery, which represented a reduction rate of 56.59%. A majority of patients (69.4%) also experienced symptom reduction of more than 50% at maximum follow-up. In addition, other tic-related outcome measures (modified Rush video-based tic rating scale, YGTSS score) and comorbidities (Yale-Brown Obsessive Compulsive Scale, Becks Depression Inventory), were also significantly reduced after deep brain stimulation.

Zhang et al. (2024) conducted a meta-analysis assessing the efficacy of DBS for Tourette syndrome and its comorbidities. (48) The analysis included 51 studies with 673 participants, focusing on the YGTSS as the primary outcome measure. DBS significantly reduced tic severity (standardized mean difference [SMD], 1.88; 95% CI, 1.74 to 2.02; p<.001; I^2=56.50%) and improved obsessive-compulsive behaviors (SMD, 0.88), depression symptoms (SMD, 1.04), and anxiety symptoms (SMD, 0.76). Subgroup analysis revealed that striatum-targeted stimulation was more effective for obsessive-compulsive symptoms than thalamic stimulation (p=.017). No significant associations were found between sex, age, or surgical target and improvements in tic, depression, or anxiety symptoms.

Randomized Controlled Trials

Key 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). (49) 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 patients receiving surgery, 14 were randomized, and 13 completed assessments after both on and off phases. For the 13 trial completers, mean YGTSS scores were 80.7 in the off-stimulation phase and 68.3 in the on-stimulation phase. The mean difference in YGTSS scores indicated an improvement of 12.4 points (95% CI, 0.1 to 24.7 points),

which was statistically significant (p=.048) after Bonferroni correction. There was no significant between-group difference in YGTSS scores for patients randomized to the on-stimulation phase first or second. Three serious adverse events were reported, 2 related to surgery and 1 related to stimulation.

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. (50) The primary endpoint was difference in YGTSS 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 YGTSS score in the active deep brain stimulation group and may, therefore, have been underpowered to detect smaller changes in YGTSS. There were no significant differences in YGTSS score change between groups (active deep brain stimulation median change, 1.1% [IQR, –23.9 to 38.1] vs. sham deep brain stimulation median change, 0.0% [IQR, –10.6 to 4.8]; p=.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 including: 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 Randomized Controlled Trials of Deep Brain Stimulation for Tourette Syndrome

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	***Comparator***
Kefalopoulou et al. (2015) (49) NCT01647269	United Kingdom	2	2009 to 2013	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	Stimulation on (Bilateral globus pallidus internus DBS)	Stimulation off

Welter et al. (2017) (50) NCT00478842	France	8	2007 to 2012	Adults aged 18 to 60 years with severe, medically refractory Tourette syndrome	n=8 anterior internal globus pallidus DBS	n=9 Sham DBS

DBS: deep brain stimulation.

Table 16. Results of Randomized Controlled Trials of Deep Brain Stimulation for Tourette Syndrome

Study	Tic Severity	Co-morbid Symptoms	Quality of Life	Depression Symptoms	Serious Adverse Events
Kefalopoulou et al. (2015) (49)[a]	YGTSS, Mean (SD) at 3 months	Y-BOCS, Mean (SD) at 3 months	GTS-QOL, Mean (SD) at 3 months	Beck Depression Inventory, Mean (SD) at 3 months	
N	15[a]	15[a]	15[a]	15[a]	15[a]
DBS	68.3 (18.6)	12.8 (10.0)	54.3 (28.4)	21.0 (13.8)	3 (20%)
No stimulation	80.7 (12.0)	14.6 (10.3)	62.0 (24.7)	20.5 (14.3)	
Treatment effect (95% CI)	12.4 (0.1-24.7, p=0.05)	p=0.98	p=0.04	p=0.13	
Welter et al. (2017) (50)	YGTSS, Mean change (CI) at 3 months	Y-BOCS, Mean change (CI) at 3 months	SF-36, Mean change (CI) at 3 months	MADRS, Mean change at 3 months	
N	16	16	16	16	19
DBS	-4.5 (-12.5 to 0.5)	-3.5 (-6.8 to 0.3)	PCS: 6.1 (1.2 to 8.7) MCS: 10.1 (1.8 to 16.8)	-2.0 (-6.0 to 0.5)	15 serious adverse events (3 in patients who withdrew before stimulation and 6 each in the active and sham

					stimulation groups) occurred in 13 patients: infections in 4 patients, 1 electrode misplacement, 1 episode of depressive signs, and 3 episodes of increased tic severity and anxiety
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=0.39	p=0.25	PCS: p>0.99 MCS: p=0.14	p=0.25	

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

[a] Crossover design.

Table 17. Study Relevance Limitations: Randomized Controlled Trials of Deep Brain Stimulation for Tourette Syndrome

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-up[e]
Kefalopoulou et al. (2015) (49)					1. 3 months of follow-up
Welter et al. (2017) (50)					1. 3 months of follow-up

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

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5. Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

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

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Kefalopoulou et al. (2015) (49)					3. Sample size based on "practical considerations"	
Welter et al. (2017) (50)					3. Powered to detect a 30-point reduction in YGTSS in active DBS group	

DBS: deep brain stimulation; YGTSS: Yale Global Tic Severity Scale.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[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 YGTSS 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, and 1 (0.6%) had lead explantation. (51)

Section Summary: Tourette Syndrome

A number of uncontrolled studies, RCTs, and several systematic reviews have been published. Most studies, including the RCTs, had sample sizes less than 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 versus 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

The purpose of deep brain stimulation is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with cluster headache or facial pain. Deep brain stimulation 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 following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest are individuals with cluster headache or facial pain. The International Headache Society's International Classification of Headache Disorders classifies types of primary and secondary headaches. (52) A summary of cluster headache based on the International Classification of Headache Disorders criteria is 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 last 15 to 180 minutes and occur from once every other day to 8 times a day. The definition further requires for the patient to have had at least 5 such attacks with at least 1 of the following symptoms or signs ipsilateral to the headache: conjunctival injection and/or lacrimation; nasal congestion and/or rhinorrhea; eyelid edema; forehead and facial sweating; miosis and/or ptosis; or a sense of restlessness or agitation. The diagnostic criteria for episodic cluster headache require at least 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 require 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 to 40 years, and men are affected 3 times more often than women.

Interventions
The therapy being considered is deep brain stimulation.

Comparators
The following practice is currently being used to treat cluster headache and facial pain: pharmacologic therapy, botulinum toxin, or conservative therapy (e.g., diet, exercise). The standard of care treatment to stop or prevent attacks of cluster headache or migraine is medical therapy. Guideline-recommended treatments for acute cluster headache 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. Steroid injections may be used to prevent or reduce the frequency of cluster headaches. Verapamil is also frequently used for prophylaxis although the best evidence supporting its effectiveness is a placebo-controlled RCT including 30 patients.

Given the high placebo response rate in cluster 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.

<u>Study Selection Criteria</u>
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Qassim et al. (2023) reported on the results of an individual patient data meta-analysis investigating deep brain stimulation for chronic facial pain, including a total of 54 patients across 7 studies. (53) The primary endpoint was the change in pain intensity using the visual analogue scale (VAS) at a defined time-point of 3 months or less after deep brain stimulation. Based on pooled data for 34 patients, the overall reduction in VAS at 3 months was 4.64 points (standard error, 0.54 points; p<.001). The authors noted that data for follow-up beyond 3 months were not eligible for statistical analysis and presented data from individual studies descriptively.

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. (54) 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 a greater than 50% reduction in the weekly frequency of attacks.

Observational Studies

Another research group from Europe published 2 case series (potentially overlapping) on the use of deep brain stimulation for the ipsilateral posterior hypothalamus in patients with chronic cluster headache. (55, 56) Stimulation was reported to result in long-term pain relief (1 to 26 months of follow-up) without significant adverse events in 16 patients with chronic cluster headaches and 1 patient with neuralgiform headache; treatment failed in the 3 patients who had atypical facial pain.

Mandat et al. (2023) reported on 7 patients with neuropathic facial pain who underwent deep brain stimulation of the periaqueductal and periventricular gray regions. (57) Efficacy was assessed using the Numeric Pain Rating Scale (NRS) and Neuropathic Pain Symptom Inventory (NPSI) before surgery and at 3 months, 1 year, and 2 years post-surgery. Four patients had pain from ischemic stroke, 1 from hemorrhagic stroke, and 2 from craniofacial injury. Results demonstrated that the NRS score decreased by 54% at 3 months, 48% at 1 year, and 45% at 2 years. The NPSI score decreased by 38% after 3 months, 32% after 12 months, and 34% after 2 years. Authors concluded that the effectiveness of therapy decreases at the 2-year follow-up.

Section Summary: Cluster Headache and Facial Pain

A systematic review, several case series and a crossover RCT have been published on the use of deep brain stimulation for cluster headache or facial pain. The systematic review included an

individual patient data meta-analysis of 34 patients, showing a significant reduction in pain intensity at 3 months following deep brain stimulation for chronic facial pain; data for follow-up beyond 3 months were not eligible for statistical analysis. The RCT included 11 patients with severe, refractory, chronic cluster headache; there were no significant differences between groups receiving active and sham stimulation. Additional RCTs or controlled studies are needed.

Treatment-Resistant Depression

Clinical Context and Therapy Purpose

The role of deep brain stimulation in treatment of other treatment-resistant depression is also being investigated. Standard treatment modalities for treatment-resistant depression include psychotherapy, medication, and electroconvulsive therapy (ECT). However, even with a number of therapies being available, many individuals can still remain symptomatic despite treatment. As an alternative therapy option, there have been multiple trials exploring deep brain stimulation in various cerebral targets for treatment-resistant depression.

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

Populations

The population of interest is individuals with treatment-resistant depression.

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 cortex. Memory implicated structures include the fornix and nucleus basalis.

Comparators

Alternative treatments vary and generally include pharmacologic therapy, behavioral therapy, and psychotherapy. 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

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Treatment-Resistant Depression - Systematic Reviews

A variety of target areas are being investigated for use of deep brain stimulation for treatment-resistant depression. Sobstyl et al. (2022) published a systematic review of studies that evaluated deep brain stimulation to the subcallosal cingulate cortex in patients with treatment resistant depression. (58) All study designs were considered but at least 5 patients were required, and follow-up had to be a minimum of 6 months. Among the 14 studies included in the analysis (N=230), mean follow-up was 14 months (range, 6 to 24). Outcomes of interest included response and remission rates at the last follow-up visit. Using raw scores, the response rate at last follow-up was 0.57 (95% CI, 0.44 to 0.69; p=.299; I^2=60.76%) and remission rate was 0.399 (95% CI, 0.2923 to 0.5158; p=.09; I^2=42.80%).

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

Wu et al. (2021) also conducted a meta-analysis of blinded studies that compared deep brain stimulation to control (placebo or sham stimulation). (60) There were 17 studies included, with a total of 233 patients; however, the majority were open-label studies (n=15). Anatomic targets included subcallosal cingulate gyrus (n=8), ventral capsule/ventral striatum (n=2), epidural prefrontal cortical (n=2), nucleus accumbens (n=1), superior lateral branch of the medial forebrain bundle (n=2), posterior gyrus rectus (n=1) and ventral anterior limb of the interna capsule (n=1). The pooled response rate estimate for the 2 RCTs was 1.45 (95% CI, 0.50 to 4.21) and for the open-label studies it was 0.56 (95% CI, 0.43 to 0.69); there was significant heterogeneity (I^2=73.6%; p<.0001). The pooled estimate for remission rate in the open-label studies was 0.32 (95% CI, 0.25 to 0.39) with no statistical heterogeneity (I^2=30.3%; p=.127); the pooled estimate for adverse events in the open-label studies was 0.67 (95% CI, 0.54 to 0.80) with significant heterogeneity (I^2=76.8%; p<.0001).

Treatment-Resistant Depression - Controlled Trials

Ventral Capsule/Ventral Striatum

One of the studies included in the meta-analysis by Hitti et al. was 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). (61) 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=.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

Another study included in the meta-analysis by Hitti et al. was 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. (62) 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<.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 limited sample size 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 Cingulate

Not included in the meta-analysis was a study by Crowell et al. (2019) who 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. (63) 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.

Giacobbe et al. (2025) published a randomized, double-blind, sham-controlled crossover trial with 2-year follow-up evaluating deep brain stimulation of the subcallosal cingulate gyrus for treatment-resistant depression. (64) Thirty-five participants with a major depressive episode and treatment resistance completed a 6-month blinded phase, followed by an 18-month open-label phase. The primary outcome was the change in the 17-item Hamilton Depression Rating Scale score at 6 months. All groups showed improvement at 3 and 6 months; no significant differences were observed between active and sham stimulation during the randomized phase, and no significant treatment effect was found for response. During the open-label phase, participants demonstrated sustained reduction in depressive symptoms, with observed-case response rates of 65.7% at 12 months, 69.0% at 18 months, and 73.1% at 24 months. A total of 37 adverse events were reported, including 5 serious adverse events; adverse events considered possibly or definitely related to deep brain stimulation included sleep disturbance, headache, pain at the surgical incision site, system dislodgment, and hearing or visual disturbance. Despite improvement during open-label follow-up, the absence of a significant benefit in the sham-controlled phase means that the efficacy of subcallosal cingulate deep brain stimulation remains unproven.

Section Summary: Treatment-Resistant Depression

Several prospective controlled trials and meta-analyses evaluating deep brain stimulation in patients with treatment resistant depression have been published. Six different target areas have been evaluated, most commonly the subcallosal cingulate. 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 randomized, double-blind, sham-controlled crossover trial of subcallosal cingulate deep brain stimulation did not demonstrate a significant benefit for active versus sham stimulation during the 6-month blinded phase. 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

Clinical Context and Therapy Purpose

The role of deep brain stimulation in treatment of obsessive-compulsive disorder (OCD) is also being investigated. This condition can be very debilitating and cause significantly reduced quality of life for individuals. Conventional management strategies include cognitive-behavioral therapy, medications, and surgical intervention; however, response to treatment may take months, and significant improvement with these therapies is not guaranteed. Deep brain stimulation may be an alternative therapy option for individuals with treatment-refractory OCD, and some trials have explored safety and efficacy of this treatment in OCD.

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

Populations

The population of interest is individuals with 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 cortex. Memory implicated structures include the fornix and nucleus basalis.

Comparators

Alternative treatments include pharmacologic therapy, behavioral therapy, and psychotherapy. 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.

The Yale-Brown Obsessive Compulsive Scale 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.

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Review

Several systematic reviews evaluating deep brain stimulation for OCD have been published.

Cohen et al (2025) conducted an individual participant data meta-analysis of sham-controlled RCTs evaluating DBS for treatment-refractory OCD. Nine RCTs (N=91) were included; 8 studies (n=84) contributed to quantitative analysis. (65) Stimulation targets varied across studies and included the anterior limb of the internal capsule, nucleus accumbens, ventral capsule/ventral striatum, bed nucleus of the stria terminalis, and subthalamic nucleus. Active DBS was associated with a 5.08-point reduction in Yale-Brown Obsessive-Compulsive Scale (YBOCS) compared to sham (95% CI, 1.99 to 8.18; Hedges' g=.56). Heterogeneity was substantial (I^2=70%; p=.002), and the 95% prediction interval crossed zero (−3.1 to 13.2). The odds of achieving response (≥35% YBOCS decrease) were significantly higher with active DBS (OR, 4.7; 95% CI, 1.8 to 12.2). Notable adverse events during active stimulation included hypomania (14%), increased anxiety (12%), and neurological symptoms (9.3%); during sham phases, suicidal thoughts (21%) and return of OCD symptoms (14%) were reported. One completed suicide occurred during the open-label phase. GRADE certainty of evidence was rated low, downgraded for study limitations and imprecision. The review was limited by small sample sizes across all included trials (largest N=17), heterogeneity in DBS targets and optimization strategies, predominantly crossover designs with potential carryover effects, and absence of blinding checks.

Abdulbaki et al. (2025) conducted a meta-analysis of 29 studies (RCTs, prospective cohort studies, and retrospective case series) evaluating DBS for treatment-refractory OCD. (66) Stimulation targets included the anterior limb of the internal capsule, ventral capsule/ventral striatum, nucleus accumbens, subthalamic nucleus, bed nucleus of the stria terminalis, inferior thalamic peduncle, and medial dorsal/ventral anterior thalamic nuclei. Pooled analysis of 27 studies (N=323) showed significant improvement in YBOCS scores at last follow-up (MD=14.12; 95% CI, 12.43 to 15.82; p<.0001; I^2=73%). Significant improvements were also observed for anxiety (Hamilton Anxiety Rating Scale [HAM-A]: MD=10.71; 95% CI, 8.55 to 12.88; p<.00001; I^2=63%), depression (Hamilton Depression Rating Scale [HAM-D]:MD=11.14; 95% CI, 9.39 to 12.89; p<.00001; I^2=0%), and global assessment of functioning (GAF: MD=5.20; 95% CI, 4.51 to 5.89; p<.00001; I^2=99%). The meta-analysis was limited by substantial heterogeneity in the primary outcome, the inclusion of predominantly uncontrolled studies (comparing pre- vs. post-DBS rather than active vs. sham), variable stimulation targets and nomenclature across studies, and the absence of a GRADE assessment of the certainty of evidence.

Gadot et al. (2022) published a systematic review of the efficacy of deep brain stimulation for treatment-resistant OCD and comorbid depressive symptoms. (67) Studies were included if they reported patient-level data on the effect of deep brain stimulation on the Yale-Brown Obsessive-Compulsive Scale. Thirty-four studies (N=352) were included in the analysis (9 RCTs, 25 nonrandomized trials) and both study types had a low risk of bias. Median follow-up in the included studies was 24 months (IQR, 12 to 32). Outcomes of interest included mean difference and percent reduction in the scale, and responder rate (defined as ≥35% reduction in Yale-Brown Obsessive-Compulsive Scale score). Random effects modeling found that Yale-Brown Obsessive-Compulsive Scale scores decreased by a mean of 47% (14.3 points; p<.01). The response rate at last follow-up was 66% (95% CI, 57% to 74%).

Mar-Barrutia et al. (2021) evaluated both the short-term and long-term effects of deep brain stimulation for OCD and included 29 studies (n=230) for short-term response and 11 studies (n=155) for long-term responses assessment; there were 7 total RCTs included. (68) Mean follow-up duration for the short-term and long-term studies was 1.5 years and 5.3 years, respectively. The authors noted that few studies were graded as low risk of bias, and there was marked heterogeneity among the studies reviewed which makes it difficult for comparison. The primary outcome measured was the Yale-Brown Obsessive-Compulsive Scale, and the mean changes in scores from pre- to post-treatment were similar in the short-term studies (change from 33.0 to 17.2) and the long-term studies (change from 34.4 to 18.0); however, significantly more patients met criteria for response in the long-term group (70.7%) versus the short-term group (60.6%). There were 26.6% of patients in the long-term group who were classified as non-responders.

Section Summary: Obsessive-Compulsive Disorder

The literature on deep brain stimulation for OCD includes RCTs and meta-analyses. Most studies had limited sample sizes and were at high risk of bias. Studies suggest that there may be improvements in OCD symptoms after deep brain stimulation treatment but have also identified a substantial number of adverse events and the optimal target(s) has not been determined. Additional blinded controlled studies are needed to draw conclusions about the impact of deep brain stimulation on the net health benefit.

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 multiple sclerosis (MS) and chronic pain, 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 following PICO was used to select literature to inform this policy.

Populations
The population of interest are individuals with anorexia nervosa, alcohol addiction, Alzheimer disease, Huntington disease, MS, or chronic pain.

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 cortex. Memory implicated structures include the fornix and nucleus basalis.

Comparators
Alternative treatments vary by condition, and generally include pharmacologic therapy, behavioral therapy, and psychotherapy. 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.

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

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Multiple Sclerosis
Systematic Review
Brandmeir et al. (2020) reported a meta-analysis of 13 studies of deep brain stimulation for MS tremor (129 patients received deep brain stimulation and 132 received medical management). (69) Results were compared for tremor severity after deep brain stimulation versus tremor severity at baseline and were combined across different target areas (ventral intermediate nucleus of the thalamus, ventral oralis nucleus of the thalamus, ventral caudal nucleus of the thalamus, zona incerta) and different levels of evidence. Four studies were rated as level II evidence, but the studies were not randomized, and the sample size was limited, ranging from 4 to 12 patients. Meta-analysis showed an improvement in the mean tremor score of 2.86 (95% CI, 2.03 to 3.70; p<.001). However, heterogeneity was high, suggesting that meta-analysis is not

appropriate, and no distinction was made for the different anatomical targets. There was also evidence of publication bias.

Observational Studies
Chagot et al. (2023) reported on a retrospective study of 104 patients with MS tremor who underwent deep brain stimulation. (70) Three months after the intervention, data were available for 89 patients, of which 57 patients (64%) had clinical and functional improvement; 26 patients had limited improvement, and 6 patients had no improvement. Of the 57 patients who had clinical improvement at 3 months, 53 patients had sustained improvement at 1 year and 25 patients had sustained improvement at 5 years.

Subsection Summary: Multiple Sclerosis
The literature on deep brain stimulation for MS tremor is characterized by a few non-randomized trials with a limited sample size and a variety of brain targets. Only 1 of the controlled trials was conducted in the last decade. In addition to these limitations, there is evidence of publication bias in meta-analysis. Literature does not currently support deep brain stimulation for MS tremor.

Chronic Pain
Systematic Review
Deer et al. (2020) conducted a systematic review of deep brain stimulation for chronic pain. (71) They identified 1 RCT from 2017 that included 10 patients with post-stroke pain syndrome and 1 RCT from 2010 with 11 patients who had chronic cluster headaches (described above). Three early case series (1990 to 2017, n=12 to 48) included patients with a variety of pain conditions, including phantom limb pain, cancer, brachial plexus injury, failed back surgery, and spinal cord injury. The location of the stimulation was variable. Publication bias was not assessed.

Subsection Summary: Chronic Pain
Literature on deep brain stimulation for chronic pain is characterized by older studies (2 RCTs and 3 case series), published between 1990 and 2017, with a wide range of pain conditions and variety of targets. A systematic review of the evidence did not evaluate publication bias, which is suggested by the low number and age of publications.

Alcohol Use Disorder
Randomized Controlled Trial
Bach et al. (2023) conducted a multicenter, double-blind, RCT of deep brain stimulation to the nucleus accumbens in 12 patients with treatment-resistant alcohol use disorder. (72) Deep brain stimulation was compared to sham stimulation over a 6-month period in hospitalized patients, followed by 12 months of unblinded treatment with deep brain stimulation in all patients. The primary outcome, continuous abstinence (i.e., time to first alcohol use), was not significantly different between groups (p=.619), likely due to limited sample size/lack of power to find a difference. Secondary outcomes, including proportion of days abstinent (p=.048), alcohol craving as measured by the Alcohol Urge Questionnaire (p=.02), and anhedonia as

measured by the Snaith-Hamilton Pleasure Scale (p=.028) were improved at 6 months with the deep brain stimulation group compared to sham stimulation. The authors stated that larger studies are needed to confirm these results.

Subsection Summary: Alcohol Use Disorder
A RCT in patients with alcohol use disorder did not find a difference in time to first alcohol use. Larger studies are needed to confirm the efficacy of deep brain stimulation in this population.

Other Indications
An exploratory study of the safety and tolerability of deep brain stimulation of the nucleus basalis of Meynert in 6 patients with dementia with Lewy bodies was reported by Gratwicke et al. (2020). (73) Clinical outcomes were not evaluated.

A pooled analysis by Shaffer et al. (2023) of observational cohorts and case reports (n=36) of deep brain stimulation in patients with anorexia nervosa stated that there may be a benefit for deep brain stimulation to the subcallosal cingulate cortex in this population. (74)

The evidence on use of deep brain stimulation for Alzheimer disease and Huntington disease consists of 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 (QOL), and treatment-related morbidity. Early studies suggest 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 these conclusions and found that tremors were effectively controlled 5 to 6 years after deep brain stimulation. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have symptoms (e.g., speech, motor fluctuations) associated with Parkinson disease (advanced or >4 years in duration with early motor symptoms) who receive 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, QOL, and treatment-related morbidity. One of the systematic reviews concluded that studies evaluating deep brain stimulation of the globus pallidus interna or subthalamic nucleus have consistently demonstrated clinically significant improvements in outcomes (e.g., neurologic function), as well as significantly better outcomes after deep brain stimulation than after a control intervention. An RCT in patients with levodopa-responsive Parkinson disease of at least 4 years in duration and uncontrolled motor symptoms found that QOL at 2 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 1 type of stimulation is superior to the other. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with symptoms associated with Parkinson disease who receive adaptive deep brain stimulation of the globus pallidus interna or subthalamic nucleus, the evidence includes one RCT. Relevant outcomes are symptoms, functional outcomes, QOL, and treatment-related morbidity. There is currently one ongoing RCT assessing the feasibility and efficacy of adaptive deep brain stimulation (aDBS) for control of Parkinson disease symptoms. One RCT assessed the feasibility and efficacy of adaptive deep brain stimulation for control of Parkinson disease symptoms. The primary efficacy outcome measured "On" time without dyskinesia, with success rates of 78.9% for single-threshold aDBS and 91% for dual-threshold aDBS. Extended follow-up demonstrated sustained benefits with dual-threshold aDBS showing additional improvements. Safety analysis showed that overall, 78.8% of patients experienced adverse events, 56.5% had device-related events, and 17.6% had serious adverse events, including one participant with 2 severe device-related injuries. The evidence is insufficient to determine that the technology results in an 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, QOL, and treatment-related morbidity. A pooled analysis of 24 studies, mainly uncontrolled, found improvements in motor scores and disability scores after 6 months and at last follow-up (mean, 32 months). Both double-blind RCTs found that severity scores improved more after active than after sham stimulation. The evidence is sufficient to determine that the technology results in an 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, QOL, and treatment-related morbidity. The RCT did not report statistically significant improvement in the dystonia severity outcomes, or the secondary outcomes related to disability and QOL, but these may have been underpowered. Additional studies, especially RCTs or other controlled studies, are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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, QOL, and treatment-related morbidity. A meta-analysis of 49 studies reported mean seizure reductions of approximately 62% to 69% across anterior nucleus of the thalamus and centromedian nucleus targeted deep brain stimulation, with responder rates of approximately 62% to 69%; seizure freedom rates were low for both targets. The majority of included studies were nonrandomized and uncontrolled, and there was substantial

heterogeneity across studies. Two RCTs with more than 15 patients were identified. The first RCT (N=110) 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 QOL 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 second RCT (N=16) showed a benefit with deep brain stimulation. Many 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 that the technology results in an improvement in the net health outcome.

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, QOL, 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 versus sham at 3 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 that the technology results in an improvement in the net health outcome.

For individuals who have cluster headaches or facial pain who receive deep brain stimulation, the evidence includes a systematic review, randomized crossover study, and case series. Relevant outcomes are symptoms, functional outcomes, QOL, and treatment-related morbidity. The systematic review included an individual patient data meta-analysis of 34 patients, showing a significant reduction in pain intensity at 3 months following deep brain stimulation for chronic facial pain; data for follow-up beyond 3 months were not eligible for statistical analysis. In an RCT of 11 patients with severe, refractory, chronic cluster headache, 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 that the technology results in an improvement in the net health outcome.

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, QOL, and treatment-related morbidity. A number of case series and several prospective controlled trials evaluating deep brain stimulation 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. 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. More recently, a randomized, double-blind, sham-controlled crossover trial of subcallosal cingulate deep brain stimulation did not demonstrate a significant benefit for active versus sham stimulation during the 6-month blinded phase, despite sustained improvement during the subsequent 18-month open-label follow-up. 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 that the technology results in an improvement in the net health outcome.

For individuals who have obsessive-compulsive disorder who receive deep brain stimulation, the evidence includes meta-analyses of RCTs. Relevant outcomes are symptoms, functional outcomes, QOL, and treatment-related morbidity. Among the RCTs on deep brain stimulation for obsessive-compulsive disorder included in meta-analyses, only 1 has reported an outcome of 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 that the technology results in an improvement in the net health outcome.

For individuals who have other neurologic or psychiatric disorders who receive deep brain stimulation, the evidence includes a number of nonrandomized studies or RCTs in patients with multiple sclerosis, chronic pain, or alcohol use disorder. Relevant outcomes are symptoms, functional outcomes, QOL, and treatment-related morbidity. One RCT with 10 multiple sclerosis patients, 2 RCTs in patients with chronic pain, and 1 RCT in patients with treatment-refractory alcohol use disorder is insufficient evidence on which to draw conclusions about the efficacy of deep brain stimulation in these populations. Additional trials are required. For individuals who have anorexia nervosa, Alzheimer disease, Huntington disease, or chronic pain who receive deep brain stimulation, the evidence includes case series; RCTs are needed to evaluate the efficacy of deep brain stimulation for these conditions. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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, which were reaffirmed in 2022. (75) This update did not change the conclusions and recommendations of the AAN (2005) practice parameters on deep brain stimulation for essential tumor. (76) 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 versus 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
In 2018, the AAN affirmed the guideline developed by the Congress of Neurological Surgeons (see Table 19). (77)

Tourette Syndrome
Guidelines from AAN (2019, reaffirmed 2022) provide recommendations on the assessment for and use of deep brain stimulation in adults with severe, treatment-refractory tics. (78) The 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. The AAN concludes that deep brain stimulation of the anteromedial globus pallidus is possibly more likely than sham stimulation to reduce tic severity.

<u>American Society for Stereotactic and Functional Neurosurgery</u>
Obsessive-Compulsive Disorder
In 2021, the American Society for Stereotactic and Functional Neurosurgery and the Congress of Neurological Surgeons updated their 2014 guidelines on deep brain stimulation for obsessive-compulsive disorder. (79) 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 or bed nucleus of stria terminalis deep brain stimulation for medically refractory obsessive-compulsive disorder. It also concluded that the evidence on unilateral deep brain stimulation was insufficient.

Refractory Epilepsy
In 2022, the American Society for Stereotactic and Functional Neurosurgery published a position statement on deep brain stimulation for medication-refractory epilepsy. (80) Indications for deep brain stimulation include confirmed diagnosis of epilepsy (focal onset seizures with or without generalization), failure to achieve seizure control after 2 or more appropriately dosed seizure medications, seizures with localized onset in a region that cannot be resected or for which surgical resection has failed, or focal-onset seizures with a nonlocalized or unclear region of onset.

<u>Congress of Neurologic Surgeons</u>
Parkinson Disease

In 2018, evidence-based guidelines from the Congress of Neurologic Surgeons, affirmed by the AAN, 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. (77)

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

Goal	Most Effective Area of Stimulation (subthalamic nucleus or globus pallidus internus)	Level of Evidence
Improving motor symptoms	subthalamic nucleus or globus pallidus internus are similarly effective	I
Reduction of dopaminergic medication	subthalamic nucleus	I
Treatment of "on" medication dyskinesias	globus pallidus internus if reduction of medication is not anticipated	I
Quality of life	no evidence to recommend one over the other	I
Lessen impact of DBS on cognitive decline	globus pallidus internus	I
Reduce risk of depression	globus pallidus internus	I
Reduce adverse effects	insufficient evidence to recommend one over the other	Insufficient

DBS: Deep brain stimulation

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. (81) 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. (82) 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 (e.g., cluster headaches) was "limited and inconsistent, and the evidence on safety shows that there were serious but well-known adverse effects." (83)

Refractory Epilepsy
In 2020, guidance from NICE indicated that the evidence on the efficacy and safety of deep brain stimulation for refractory epilepsy (for anterior thalamic targets) was limited in both quantity and quality, and "this procedure should only be used with special arrangements for clinical governance, consent, and audit or research." (84) For targets other than the anterior thalamus, NICE recommends that "this procedure should only be used in the context of research."

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." (85) The guidance noted that deep brain stimulation should only be offered when Parkinson disease is refractory to best medical treatment.

Medicare National Coverage
Effective for services furnished in April 2003, Medicare covers unilateral or bilateral thalamic ventralis intermedius nucleus deep brain stimulation for the treatment of essential tumor and/or parkinsonian tremor and unilateral or bilateral subthalamic nucleus or globus pallidus interna deep brain stimulation for the treatment of Parkinson disease when the following conditions are met (86):

1. Devices must be approved by the Food and Drug Administration (FDA) for "deep brain stimulation or devices used in accordance with FDA-approved protocols governing Category B Investigational Device Exemption (IDE) deep brain stimulation clinical trials."
2. For thalamic ventralis intermedius nucleus deep brain stimulation, patients must meet all of the following criteria:
    a) "Diagnosis of ET [essential tremor] based on postural or kinetic tremors of hand(s) without other neurologic signs, or diagnosis of idiopathic Parkinson disease (presence of at least 2 cardinal PD [Parkinson disease] features (tremor, rigidity or bradykinesia)) which is of a tremor-dominant form.
    b) Marked disabling tremor of at least level 3 or 4 on the Fahn-Tolosa-Marin Clinical Tremor Rating Scale (or equivalent scale) in the extremity intended for treatment, causing significant limitation in daily activities despite optimal medical therapy.
    c) Willingness and ability to cooperate during conscious operative procedure, as well as during postsurgical evaluations, adjustments of medications and stimulator settings."
3. For subthalamic nucleus or globus pallidus interna deep brain stimulation, patients must meet all of the following criteria:

a) “Diagnosis of PD based on the presence of at least 2 cardinal Parkinson disease features (tremor, rigidity or bradykinesia).
b) Advanced idiopathic PD as determined by the use of Hoehn and Yahr stage or Unified Parkinson's Disease Rating Scale part III motor subscale.
c) L-dopa responsive with clearly defined ‘on’ periods.
d) Persistent disabling Parkinson’s symptoms or drug side effects (e.g., dyskinesias, motor fluctuations, or disabling ‘off’ periods) despite optimal medical therapy.
e) Willingness and ability to cooperate during conscious operative procedure, as well as during post-surgical evaluations, adjustments of medications and stimulator settings.”

Deep brain stimulation is not covered for essential tumor or Parkinson disease patients with any of the following:
1. “Non-idiopathic Parkinson's disease or ‘Parkinson’s Plus’ syndromes.
2. Cognitive impairment, dementia or depression, which would be worsened by or would interfere with the patient's ability to benefit from DBS [deep brain stimulation].
3. Current psychosis, alcohol abuse or other drug abuse.

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

Previous movement disorder surgery within the affected basal ganglion.

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

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this policy are listed in Table 20. Trials of deep brain stimulation for Parkinson disease were excluded.

Table 20. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Ongoing			
Epilepsy			
NCT03900468[a]	Medtronic Deep Brain Stimulation Therapy for Epilepsy Post-Approval Study (EPAS)	140	Mar 2026
NCT06248333	Subthalamic Nucleus Electrical Stimulation for Drug-resistant Focal Motor Epilepsy (STEM)	33	Jun 2026
NCT06364085	EPI-BOOST: Enhancing Epilepsy Management With Precision Deep Brain Stimulation	40	Jun 2026

NCT07010276	Centromedian Deep Brain Stimulation vs. Vagus Nerve Stimulation for the Treatment of Drug-Resistant Epilepsy and Epileptic Spasms in Children: A Randomized Trial	20	Dec 2027
Obsessive-Compulsive Disorder			
NCT02773082[a]	Reclaim Deep Brain Stimulation Therapy for Obsessive-Compulsive Disorder (OCD)	50	Jan 2030
NCT02844049	European Study of Quality of Life in Resistant OCD Patients Treated by subthalamic nucleus deep brain stimulation	60	Apr 2027
NCT05995951	Deep Brain Stimulation Surgery for the Treatment of Refractory Obsessive-Compulsive Disorder	10	Sept 2025
NCT07031544	Efficacy and Influencing Factors of Combined Anterior Limb of Internal Capsule and Nucleus Accumbens Deep Brain Stimulation in Treatment-Refractory Obsessive-Compulsive Disorder	60	Mar 2027
Treatment Resistant Depression			
NCT03653858[a]	Controlled Randomized Clinical Trial to Assess Efficacy of Deep Brain Stimulation of the slMFB in Patients with Treatment Resistant Major Depression (FORSEEIII)	47	Jun 2025 (unknown)
NCT06096207	DBS for Depression	20	Oct 2038
Alzheimer Disease			
NCT05882344	Deep Brain Stimulation for Alzheimer’s	2	Oct 2028
Unpublished			
NCT02076698	Deep Brain Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy	62	Nov 2021 (completed)
NCT04181229	Deep Brain Stimulation After Failed Vagal Nerve Stimulation for the Treatment of Drug-Resistant Epilepsy in Children	25	Aug 2023 (completed)
NCT05762926	Non-invasive Brain Stimulation by Transcranial Pulse Stimulation as a Coadjunctive Treatment in Alzheimer's Disease	50	May 2024 (unknown)
NCT03622905	ADvance II Study: DBS-f in Patients With Mild Alzheimer's Disease	74	Feb 2024 (completed)
NCT03653858[a]	Controlled Randomized Clinical Trial to Assess Efficacy of Deep Brain Stimulation of the slMFB in Patients With Treatment Resistant	47	Jun 2025 (unknown)

	Major Depression (FORSEEIII)		
NCT04244513[a]	Deep Brain Stimulation Treatment for Chorea in Huntington's Disease	40	Dec 2023 (unknown)
NCT04164056	Hippocampal and Thalamic deep brain stimulation for Bilateral Temporal Lobe Epilepsy	80	Sep 2024 (unknown)

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	61850, 61863, 61864, 61867, 61868, 61885, 61886, 95970, 95983, 95984
HCPCS Codes	C1767, L8679, L8680, L8685, L8686, L8687, L8688

*Current Procedural Terminology (CPT®) ©2025 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been changed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
09/15/2026	Document updated. Coverage unchanged. Added references 20, 26, 32, 64-66; others updated and/or removed.
01/01/2026	Document updated with literature review. The following changes were made to Coverage: 1) Added "Adaptive deep brain stimulation for Parkinson disease is considered experimental, investigational and/or unproven (see Policy Guidelines)"; and 2) Modified coverage from "seven years of age and older" to "older than 7 years seven years of age" in individuals with chronic, intractable (drug-refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, or cervical dystonia (torticollis). Added references 18, 19, 37 and 48.
02/01/2025	Document updated with literature review. Editorial changes only made to Coverage, without change in intent. References 5, 37, 38, 49, 53, and 65 added; others removed.
01/01/2024	Document updated with literature review. Coverage unchanged. References 5, 22-25, 27-36, 56, 64, 66, 70-71, 76, 78, 83-84, and 90 added; others removed.

12/01/2022	Reviewed. No changes.
11/01/2021	Document updated with literature review. Coverage unchanged. References 21, 54, 57-58, 60-62, 65, and 67 added; some updated and others removed.
07/15/2020	Reviewed. No changes.
09/15/2019	Document updated with literature review. Coverage unchanged. References 6-9, 23-24, 26, 29-34, 36-38, 40, 47-49, and 68 were added.
06/15/2018	Reviewed. No changes.
08/15/2017	Document updated with literature review. The following changes were made to Coverage: 1) In medically necessary statement on unilateral or bilateral deep brain stimulation of the globus pallidus or subthalamic nucleus, "OR Parkinson disease for at least 4 years" added to medically necessary criteria for use in Parkinson disease; and 2) Tardive dyskinesia added as an example on list of experimental, investigational, and/or unproven indications.
12/01/2016	Document updated with literature review. The following statement was added to the coverage statement: "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 addition the following 2 Notes were added: 1) Disabling, medically unresponsive tremor is defined as all of the following: tremor causing significant limitation in daily activities and inadequate control by maximal dosage of medication for at least 3 months before implant and 2) Contraindications to deep brain stimulation include: patients who: are not good surgical risks because of unstable medical problems or because of the presence of a cardiac pacemaker; have medical conditions that require repeated magnetic resonance imaging (MRI); have dementia that may interfere with the ability to cooperate; or have had botulinum toxin injections within the last 6 months.
06/01/2015	Document updated with literature review. The following indications were added under the experimental, investigational and/or unproven coverage statement: psychiatric or neurologic disorders including but not limited to: depression, obsessive-compulsive disorder, alzheimer disease, anorexia nervosa, alcohol addiction, or chronic pain. Title changed from Deep Brain Stimulation for Tremor. CPT/HCPCS code(s) updated
06/01/2011	CPT/HCPCS code(s) updated
08/15/2009	Revised and updated entire document with literature search and no coverage change. This policy is no longer scheduled for routine literature review and update.
07/01/2009	CPT/HCPCS code(s) updated
05/01/2008	CPT/HCPCS code(s) updated
12/01/2007	CPT/HCPCS code(s) updated
09/01/2007	Revised/Updated Entire Document
01/01/2006	Codes Revised/Added/Deleted
05/15/2005	Revised/Updated Entire Document

11/01/2004	Codes Revised/Added/Deleted
02/01/2002	Codes Revised/Added/Deleted
11/01/2000	New Medical Document