The services described in Oxford policies are subject to the terms, conditions and limitations of the Member's contract or certificate. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage enrollees. Oxford reserves the right, in its sole discretion, to modify policies as necessary without prior written notice unless otherwise required by Oxford's administrative procedures or applicable state law. The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies.

Certain policies may not be applicable to Self-Funded Members and certain insured products. Refer to the Member's plan of benefits or Certificate of Coverage to determine whether coverage is provided or if there are any exclusions or benefit limitations applicable to any of these policies. If there is a difference between any policy and the Member’s plan of benefits or Certificate of Coverage, the plan of benefits or Certificate of Coverage will govern.

## CONDITIONS OF COVERAGE

<table>
<thead>
<tr>
<th>Applicable Lines of Business/Products</th>
<th>This policy applies to Oxford Commercial plan membership</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefit Type</td>
<td>General benefits package</td>
</tr>
<tr>
<td>Referral Required (Does not apply to non-gatekeeper products)</td>
<td>No</td>
</tr>
<tr>
<td>Authorization Required (Precertification always required for inpatient admission)</td>
<td>Yes&lt;sup&gt;1,3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Precertification with Medical Director Review Required</td>
<td>Yes&lt;sup&gt;1,2,3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Applicable Site(s) of Service (If site of service is not listed, Medical Director review is required)</td>
<td>Inpatient, Outpatient, Office&lt;sup&gt;1,2,3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Special Considerations</td>
<td>Electronic analysis of an implanted neurostimulator pulse generator system (CPT codes 95970, 95978, 95979 and 61880 ) does not require Medical Director review in any setting, and does not require precertification when performed in the office setting &lt;sup&gt;2&lt;/sup&gt;Review by a Medical Director or their designee</td>
</tr>
</tbody>
</table>
Special Considerations

(continued)

is required for all codes in the policy EXCEPT for codes 61880, 95970, 95978 and 95979.

Precertification is required for services covered under the Member's General Benefits package when performed in the office of a participating provider. For Commercial plans, precertification is not required, but is encouraged for out-of-network services performed in the office that are covered under the Member's General Benefits package. If precertification is not obtained, Oxford may review for medical necessity after the service is rendered.

BENEFIT CONSIDERATIONS

Essential Health Benefits for Individual and Small Group:
For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits (“EHBs”). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs (such as maternity benefits), the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this guideline, it is important to refer to the member specific benefit document to determine benefit coverage.

COVERAGE RATIONALE

Deep brain stimulation is considered to be proven and medically necessary for treating the following:

- Idiopathic Parkinson’s disease when used according to U.S. Food and Drug Administration (FDA) indications.
- Essential tremor when used according to U.S. Food and Drug Administration (FDA) indications.
- Primary dystonia* (occurs apart from any other identifiable illness), including generalized and/or segmental dystonia, hemidystonia and cervical dystonia (torticollis) when used according to U.S. Food and Drug Administration (FDA) indications.

*Primary dystonia may include genetic torsion dystonia, acquired torsion dystonia (not due to drugs), spasmodic torticollis, fragments of torsion dystonia, and unspecified torticollis.

Deep brain stimulation is unproven and not medically necessary for treating secondary Parkinsonism (result of head trauma, metabolic conditions, toxicity, drugs or other medical disorders).
Well-designed studies demonstrating the efficacy of deep brain stimulation for treating secondary Parkinsonism are not available. Clinical trials are needed to demonstrate the benefit of deep brain stimulation for this patient population.

Deep brain stimulation is unproven and not medically necessary for treating secondary dystonia (occurs with illness, after trauma or following exposure to certain medications or toxins).
There is inadequate evidence of the safety and efficacy of deep brain stimulation for treating secondary dystonia. Questions remain with regard to patient selection criteria and long-term benefits and safety compared with standard treatments. Formal comparisons, with large randomized controlled or comparative trials of pallidotomy, thalamotomy, and deep brain stimulation, are required before conclusions can be drawn regarding the use of deep brain stimulation for patients with secondary dystonia.
Deep brain stimulation is unproven and not medically necessary for treating conditions other than those listed as medically necessary. This includes but is not limited to the following diagnoses:

- Depression
- Obsessive-compulsive disorder (OCD)
- Epilepsy
- Tourette syndrome
- Cluster headache
- Impulsive or violent behavior
- Chronic pain
- Trigeminal neuralgia
- Movement disorders caused by multiple sclerosis (MS)

Some studies have examined the use of deep brain stimulation for treating major depression, obsessive-compulsive disorder (OCD), epilepsy, Tourette syndrome, cluster headache, impulsive or violent behavior, stroke pain, chronic pain, phantom limb pain, trigeminal neuralgia and movement disorders of multiple sclerosis (MS). However, because of limited studies, small sample sizes, weak study designs and heterogenous patient characteristics, there is insufficient data to conclude that deep brain stimulation is safe and/or effective for treating these indications.

**APPLICABLE CODES**

The Current Procedural Terminology (CPT®) codes and Healthcare Common Procedure Coding System (HCPCS) codes listed in this policy are for reference purposes only. Listing of a service code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the enrollee specific benefit document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claims payment. Other policies and coverage determination guidelines may apply. This list of codes may not be all inclusive.

**Applicable CPT Codes**

<table>
<thead>
<tr>
<th>CPT® Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>61863</td>
<td>Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; first array</td>
</tr>
<tr>
<td>61864</td>
<td>Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; each additional array (List separately in addition to primary procedure)</td>
</tr>
<tr>
<td>61867</td>
<td>Twist drill, burr hole, craniotomy, or craniectomy for stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; first array</td>
</tr>
<tr>
<td>61868</td>
<td>Twist drill, burr hole, craniotomy, or craniectomy for stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; each additional array (List separately in addition to primary procedure)</td>
</tr>
<tr>
<td>61880</td>
<td>Revision or removal of intracranial neurostimulator electrodes</td>
</tr>
<tr>
<td>61885</td>
<td>Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array</td>
</tr>
<tr>
<td>61886</td>
<td>Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to 2 or more electrode arrays</td>
</tr>
</tbody>
</table>
Deep Brain Stimulation (DBS) delivers electrical pulses to the brain via electrodes surgically implanted in the internal globus pallidus internal (GPI), subthalamic nucleus (STN) or ventral intermediate nucleus (VIM) of the thalamus. The mechanism of action is not completely understood, but the goal of DBS is to interrupt the pathways responsible for the abnormal movements associated with movement disorders such as Parkinson's disease and essential tremor. The exact location of electrodes depends on the type of movement disorder. Unlike standard surgical ablation, which causes permanent destruction of the targeted area, DBS is reversible and adjustable. The DBS device consists of an implantable pulse generator (IPG) or neurostimulator, an implantable lead with electrodes and a connecting wire. The neurostimulator is approximately the size of a stop watch and is similar to a cardiac pacemaker. Subcutaneous extension wires connect the lead(s) to the neurostimulator which is implanted near the clavicle or, in the case of younger primary dystonia patients, in the abdomen.

When used according to U.S. Food and Drug Administration (FDA) indications, deep brain stimulation is used to treat selected individuals with Parkinson's disease, essential tremor, and primary dystonia. Most forms of Parkinson's disease are idiopathic (having no specific known cause). In secondary Parkinsonism, the symptoms are a result of head trauma, metabolic conditions, toxicity, drugs, or other medical disorders. Primary dystonia occurs on its own, apart from any illness. Secondary dystonia can occur with illness, after trauma or following exposure to certain medications or toxins. Types of dystonia include:

- Generalized - affects multiple areas of the body
- Focal - affects one specific area of the body, such as the neck (cervical dystonia or torticollis), eyelid (blepharospasm) or hand (writer's cramp)

### CPT® Code Description

<table>
<thead>
<tr>
<th>CPT® Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>95970</td>
<td>Electronic analysis of implanted neurostimulator pulse generator system (e.g., rate, pulse amplitude, pulse duration, configuration of wave form, battery status, electrode selectability, output modulation, cycling, impedance and patient compliance measurements); simple or complex brain, spinal cord, or peripheral (i.e., cranial nerve, peripheral nerve, sacral nerve, neuromuscular) neurostimulator pulse generator/transmitter, without reprogramming</td>
</tr>
<tr>
<td>95978</td>
<td>Electronic analysis of implanted neurostimulator pulse generator system (e.g., rate, pulse amplitude and duration, battery status, electrode selectability and polarity, impedance and patient compliance measurements), complex deep brain neurostimulator pulse generator/transmitter, with initial or subsequent programming; first hour</td>
</tr>
<tr>
<td>95979</td>
<td>Electronic analysis of implanted neurostimulator pulse generator system (e.g., rate, pulse amplitude and duration, battery status, electrode selectability and polarity, impedance and patient compliance measurements), complex deep brain neurostimulator pulse generator/transmitter, with initial or subsequent programming; each additional 30 minutes after first hour (List separately in addition to code for primary procedure)</td>
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</table>

### Applicable HCPCS Codes

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>L8679</td>
<td>Implantable neurostimulator, pulse generator, any type</td>
</tr>
<tr>
<td>L8680</td>
<td>Implantable neurostimulator electrode (with any number of contact points), each</td>
</tr>
<tr>
<td>L8682</td>
<td>Implantable neurostimulator radiofrequency receiver</td>
</tr>
<tr>
<td>L8683</td>
<td>Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver</td>
</tr>
<tr>
<td>L8685</td>
<td>Implantable neurostimulator pulse generator, single array, rechargeable, includes extension</td>
</tr>
<tr>
<td>L8687</td>
<td>Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension</td>
</tr>
</tbody>
</table>

### DESCRIPTION OF SRVICES

Deep brain stimulation (DBS) delivers electrical pulses to the brain via electrodes surgically implanted in the internal globus pallidus internal (GPI), subthalamic nucleus (STN) or ventral intermediate nucleus (VIM) of the thalamus. The mechanism of action is not completely understood, but the goal of DBS is to interrupt the pathways responsible for the abnormal movements associated with movement disorders such as Parkinson's disease and essential tremor. The exact location of electrodes depends on the type of movement disorder. Unlike standard surgical ablation, which causes permanent destruction of the targeted area, DBS is reversible and adjustable. The DBS device consists of an implantable pulse generator (IPG) or neurostimulator, an implantable lead with electrodes and a connecting wire. The neurostimulator is approximately the size of a stop watch and is similar to a cardiac pacemaker. Subcutaneous extension wires connect the lead(s) to the neurostimulator which is implanted near the clavicle or, in the case of younger primary dystonia patients, in the abdomen.

When used according to U.S. Food and Drug Administration (FDA) indications, deep brain stimulation is used to treat selected individuals with Parkinson's disease, essential tremor, and primary dystonia. Most forms of Parkinson's disease are idiopathic (having no specific known cause). In secondary Parkinsonism, the symptoms are a result of head trauma, metabolic conditions, toxicity, drugs, or other medical disorders. Primary dystonia occurs on its own, apart from any illness. Secondary dystonia can occur with illness, after trauma or following exposure to certain medications or toxins. Types of dystonia include:

- Generalized - affects multiple areas of the body
- Focal - affects one specific area of the body, such as the neck (cervical dystonia or torticollis), eyelid (blepharospasm) or hand (writer's cramp)
Deep brain stimulation has been proposed for treating other disorders such as major depression, epilepsy, Tourette syndrome, cluster headache, impulsive or violent behavior, chronic pain and trigeminal neuralgia, phantom limb pain, and movement disorders of multiple sclerosis.

**CLINICAL EVIDENCE**

**Parkinson’s Disease & Essential Tremor**
Evidence from available published studies indicates that deep brain stimulation (DBS) provides clinically and statistically significant improvements in patients with Parkinson’s disease (PD) and essential tremor (ET).

In a meta-analysis of randomized controlled trials (RCTs), Perestelo-Perez et al. (2014) described the efficacy of DBS in improving motor signs, functionality and quality of life of PD patients. Six RCTs (n = 1,184) that compared DBS plus medication versus medication alone were included in the analysis. The results showed that DBS significantly improves patients’ symptoms, functionality and quality of life. Effects sizes are intense for the reduction of motor signs and improvement of functionality in the off-medication phase, in addition to the reduction of the required medication dose and its associated complications. Moderate effects were observed in the case of motor signs and time in good functionality in the on-medication phase, in addition to the quality of life. Although the number of RCTs obtained is small, the total sample size is relatively large, confirming the efficacy of DBS in the control of motor signs and improvement of patients’ functionality and quality of life.

Liu et al. (2014) performed a meta-analysis that compared the efficacy of DBS in the globus pallidus internus (GPI) and the subthalamic nucleus (STN) regions for patients with advanced Parkinson disease (PD). Six eligible trials containing a total of 563 patients were included in the analysis. The Unified Parkinson’s Disease Rating Scale Section II (UPDRS Section II - activities of daily living) scores for patients on medication improved equally in both DBS groups (p = 0.97). STN DBS allowed medication dosages to be reduced more than GPI DBS. Psychiatric symptoms, measured by Beck Depression Inventory, 2nd edition scores, showed greater improvement from baseline after GPI DBS than after STN DBS. The authors concluded that GPI and STN DBS improve motor function and activities of daily living for PD patients. Differences in therapeutic efficacy for PD were not observed between the 2 procedures. STN DBS allowed greater reduction in medication for patients, whereas GPI DBS provided greater relief from psychiatric symptoms. According to the authors, an understanding of other symptomatic aspects of targeting each region and long-term observations on therapeutic effects are needed.

To assess the current state of knowledge on essential tremor (ET) therapy and make recommendations based on the analysis of evidence, Zappia et al. (2013) reviewed the literature regarding pharmacologic and surgical therapies, providing a quality assessment of the studies and the strength of recommendations for each treatment. A systematic literature review was performed to identify all the studies conducted on patients with ET. Based on the results of the review, thalamic deep-brain stimulation was recommended for refractory ET.

**Professional Societies**

**American Academy of Neurology (AAN):**
In a practice parameter for the treatment of Parkinson’s disease, the AAN recommends the following:

- DBS of the subthalamic nucleus (STN) may be considered as a treatment option in PD patients to improve motor function and to reduce motor fluctuations, dyskinesia, and medication usage (Level C - possibly effective, ineffective, or harmful for the given condition in the specified population). Patients need to be counseled regarding the risks
and benefits of this procedure. There is insufficient evidence to make any recommendations about the effectiveness of DBS of the GPi or ventralis intermedius (VIM) nucleus of the thalamus in reducing motor complications or medication usage, or in improving motor function in PD patients (Level U - data inadequate or conflicting given current knowledge, treatment is unproven).

- Preoperative response to levodopa should be considered as a factor predictive of outcome after DBS of the STN (Level B - probably effective, ineffective, or harmful for the given condition in the specified population). Age and duration of PD may be considered as factors predictive of outcome after DBS of the STN. Younger patients with shorter disease durations may possibly have improvement greater than that of older patients with longer disease durations (Level C). There is insufficient evidence to make any recommendations about factors predictive of improvement after DBS of the GPi or VIM nucleus of the thalamus in PD patients. (Level U). (Pahwa, 2006)

In a practice parameter for essential tremor therapies, the AAN recommends the following:

- DBS of the VIM thalamic nucleus may be used to treat medically refractory limb tremor in essential tremor (Level C - possibly effective, ineffective, or harmful for the given condition in the specified population).
- There is insufficient evidence to make recommendations regarding the use of thalamic DBS for head or voice tremor (Level U - data inadequate or conflicting given current knowledge, treatment is unproven).
- DBS has fewer adverse events than thalamotomy (Level B - probably effective, ineffective, or harmful for the given condition in the specified population). However, the decision to use either procedure depends on each patient's circumstances and risk for intraoperative complications compared to feasibility of stimulator monitoring and adjustments. (Zesiewicz, 2005)

The AAN issued an update of the 2005 American Academy of Neurology practice parameter on the treatment of essential tremor (ET) in 2011. Conclusions and recommendations for deep brain stimulation (Level C, possibly effective) were unchanged from the previous guideline. The guideline indicated that there were no additional trials (published between 2004 and April 2010) rated better than Class IV that examined the efficacy and safety of deep brain stimulation (DBS) of the thalamus for the treatment of ET (Zesiewicz, 2011).

Dystonia

Evidence from available published controlled trials and case series indicates that deep brain stimulation provides improvement in movement symptoms in patients with primary dystonia (Volkmann et al. 2015; Sarubbo et al. 2012; Vidailhet et al. 2007; Houeto et al. 2007).

In a controlled multicentre trial, Volkmann et al. (2013) assessed the safety and efficacy of pallidal neurostimulation in patients with primary generalized or segmental dystonia who were prospectively followed up for 5 years. Forty patients were randomly assigned to either sham neurostimulation or neurostimulation of the internal globus pallidus for a period of 3 months and thereafter all patients completed 6 months of active neurostimulation. A total of 38 patients agreed to be followed up annually after the activation of neurostimulation, including assessments of dystonia severity, pain, disability, and quality of life. An intention-to-treat analysis including all patients from the parent trial showed significant improvements in dystonia severity at 3 years and 5 years compared with baseline. The improvement from 6 months to 3 years was significant and sustained at the 5-year follow-up. The authors concluded that 3 years and 5 years after surgery, pallidal neurostimulation continues to be an effective and relatively safe treatment option for patients with severe idiopathic dystonia. This long-term observation provides further evidence.

Andrews et al. (2010) analyzed combined published results of individual patient outcomes following DBS for all types of dystonia. Data was available in 157 studies for 466 patients with all forms of dystonia. The subclassification of these patients included 344 with primary forms of dystonia, 10 with myoclonus dystonia, 19 with heredodegenerative dystonias and 93 who had DBS for secondary dystonia. Patients with primary forms of dystonia, myoclonus dystonia,
subtypes of heredodegenerative dystonia and tardive dystonia have a greater than 50% mean improvement in dystonia severity following DBS. Among patients with primary generalized dystonia, multiple regression analysis showed that a shorter duration of symptoms, a lower baseline severity score and DYT1 positive status were all independently associated with a significantly higher percentage improvement from surgery. Patients with other forms of heredodegenerative and secondary dystonia have variable responses, making prediction of response in future patients difficult.

Koy et al. (2013) performed a meta-analysis and analyzed the published literature regarding deep brain stimulation and secondary dystonia to evaluate the effect on cerebral palsy, a common cause of secondary dystonia. Twenty articles that included 68 patients with cerebral palsy undergoing deep brain stimulation assessed by the Burke-Fahn-Marsden Dystonia Rating Scale were identified. Most articles were case reports reflecting great variability in the score and duration of follow-up. The mean Burke-Fahn-Marsden Dystonia Rating Scale movement score was 64.94 ± 25.40 preoperatively and dropped to 50.5 ± 26.77 postoperatively, with a mean improvement of 23.6% at a median follow-up of 12 months. There was a significant negative correlation between severity of dystonia and clinical outcome. The authors concluded that deep brain stimulation can be an effective treatment option for dyskinetic cerebral palsy. The authors stated that in view of the heterogeneous data, a prospective study with a large cohort of patients in a standardized setting with a multidisciplinary approach would be helpful in further evaluating the role of deep brain stimulation in cerebral palsy.

In a systematic review, Mentzel et al. (2012) assessed the efficacy and safety, specifically the psychiatric side effects, of DBS in patients with medication-induced tardive dyskinesia and dystonia (TDD) (a form of secondary dystonia). Seventeen studies involving 50 patients with TDD who underwent DBS were included in the review. The mean improvement of TDD of the combined patients 3 to 76 months after implantation was 77.5% on the Burke-Fahn-Marsden Dystonia Rating Scale. Of the 50 patients, 1 experienced an exacerbation of depression, and 1 experienced an exacerbation of psychosis. The authors concluded that DBS seems to be effective and relatively safe for patients with treatment-resistant TDD; however, the results should be interpreted with caution, as most of the data are from case reports and small trials.

Kim et al. (2011) applied a multimodal method to maximize the treatment effects of deep brain stimulation in patients with secondary dystonia. Four patients underwent bilateral globus pallidus internus (GPI) deep brain stimulation (DBS) and six patients underwent bilateral GPI DBS plus unilateral thalamotomy for treatment of cerebral palsy (CP). Among the patients with secondary dystonia without CP, five were also treated by DBS. Patients with generalized secondary dystonia with cerebral palsy were classified into group I and patients with focal dystonia without CP into group II. The movement and disability scores of group I-A had improved by 32.0% and 14.3%, respectively, at the last follow-up compared with baseline. The movement and disability scores of group I-B had improved by 31.5% and 0.18% at the last follow-up compared with baseline, respectively. In comparison with patients in group I-A, patients in group I-B showed a significant improvement in movement scores for the contralateral arm. Group II patients showed a marked improvement in movement and disability scores of 77.7% and 80.0%, respectively. The authors concluded that DBS plus unilateral ventralis oralis thalamotomy for CP patients with fixed states in the upper extremities is useful not only to treat secondary dystonic movement but also to improve quality of life. The authors concluded that excellent clinical outcomes were achieved using DBS in group II patients with post-traumatic dystonia and tardive dyskinesia. However, the conclusions that can be drawn from this study are limited by the extremely small number of study participants. These findings require confirmation in a larger study.

The National Institute for Health and Care Excellence (NICE) issued a guidance stating that the current evidence supports the safety and efficacy of DBS as a treatment modality for dystonia. Dystonia may be treated conservatively or surgically. Conservative treatment only treats the symptoms, and surgical intervention (i.e., thalamotomy and pallidotomy) may not render long-term benefits. Patient selection and management should be managed by a multidisciplinary team specializing in the long-term care of patients with movement disorders. (NICE, 2006)
**Professional Societies**

**European Federation of Neurological Societies:**
The European Federation of Neurological Societies Guidelines on Diagnosis and Treatment of Primary Dystonias state that pallidal deep brain stimulation is considered a good option, particularly for primary generalized or cervical dystonia, after medication or botulinum toxin have failed. Deep brain stimulation is less effective in secondary dystonia (Albanese, 2011).

**Other Conditions**

**Tourette Syndrome**

In a randomized, double-blind, crossover trial, Kefalopoulou et al. (2015) recruited eligible patients (severe medically refractory Tourette's syndrome, age ≥20 years) from two clinics for tertiary movement disorders. Enrolled patients received surgery for globus pallidus internus (GPI) DBS and then were randomly assigned in a 1:1 ratio (computer-generated pairwise randomization according to order of enrollment) to receive either stimulation on-first or stimulation off-first for 3 months, followed by a switch to the opposite condition for a further 3 month period. Patients and rating clinicians were masked to treatment allocation; an unmasked clinician was responsible for programming the stimulation. Fifteen patients were enrolled in the study. Fourteen patients were randomly assigned and 13 completed assessments in both blinded periods (seven in the on-first group, six in the off-first group). Mean Yale Global Tic Severity Scale (YGTSS) total score in these 13 patients was 87.9 at baseline, 80.7 for the off-stimulation period, and 68.3 for the on-stimulation period. All 15 patients received stimulation in the open-label phase. Overall, three serious adverse events occurred (two infections in DBS hardware at 2 and 7 weeks postoperatively, and one episode of deep-brain-stimulation-induced hypomania during the blinded on-stimulation period); all three resolved with treatment. The authors concluded that GPI stimulation led to a significant improvement in tic severity, with an overall acceptable safety profile. According to the authors, future research should concentrate on identifying the most effective target for DBS to control both tics and associated comorbidities, and further clarify factors that predict individual patient response.

Ackermans et al. (2011) evaluated 8 patients with intractable Tourette syndrome who were included in a double-blind randomized cross-over trial assessing the efficacy and safety of deep brain stimulation of the thalamus. After surgery, the patients were randomly assigned to 3 months stimulation followed by 3 months OFF stimulation (Group A) or vice versa (Group B). The cross-over period was followed by 6 months ON stimulation. Assessments were performed prior to surgery and at 3, 6 months and 1 year after surgery. Interim analysis was performed on a sample of six male patients with only one patient randomized to Group B. Tic severity during ON stimulation was significantly lower than during OFF stimulation, with substantial improvement (37%) on the Yale Global Tic Severity Scale. The effect of stimulation 1 year after surgery was sustained with significant improvement (49%) on the Yale Global Tic Severity Scale when compared with preoperative assessments. Secondary outcome measures did not show any effect at a group level, either between ON and OFF stimulation or between preoperative assessment and that at 1 year postoperatively. Cognitive re-assessment at 1 year after surgery showed that patients needed more time to complete the Stroop Color Word Card test. Serious adverse events included one small hemorrhage ventral to the tip of the electrode, one infection of the pulse generator, subjective gaze disturbances and reduction of energy levels in all patients. According to the authors, the present preliminary findings suggest that deep brain stimulation may reduce tic severity in refractory Tourette syndrome, but there is the risk of adverse effects related to oculomotor function and energy levels. Further randomized controlled trials on other targets are needed since the search for the optimal DBS target is still ongoing.

Piedad et al. (2012) evaluated which patients with Gilles de la Tourette syndrome (GTS) should be treated with DBS and what is the best target. To answer these questions, the authors conducted a systematic literature review of the published studies of DBS in GTS and critically evaluated the current evidence for both patient and target selection. The authors found that since 1999, up to 99 cases of DBS in GTS have been reported in the scientific literature, with varying selection criteria, stimulation targets, and assessment protocols. The vast majority of studies published to date are case reports or case series reporting successful outcomes in terms of both tic severity improvement and tolerability. The reviewed studies suggest that the best candidates...
are patients with significant functional impairment related to the tic symptoms, who did not respond to conventional pharmacological and behavioral interventions. The globus pallidus internus and thalamus appear to be the safest and most effective targets, especially for patients with "pure" GTS and patients with comorbid obsessive-compulsive symptoms, anxiety, and depression. The authors concluded that DBS is a promising treatment option for severe cases of GTS. According to the authors, there is a need to reach consensus on the definition of refractory treatment and to conduct larger double-blind randomized controlled studies on the most promising targets.

Saleh et al. (2012) analyzed 33 research articles reporting on DBS in patients with Gilles de la Tourette syndrome (GTS). The review included 88 patients with Tourette's syndrome who were treated since 1999 with DBS. The majority of patients received thalamic stimulation. Significantly fewer patients were treated with globus pallidus internus stimulation. Occasionally, the anterior limb of the internal capsule and the nucleus accumbens were implanted. The subthalamic nucleus was selected once. All targets were reported with positive results, but of variable extent. The majority of studies (n = 26) met only level 4 criteria (observational studies without control), while four studies met level 1 criteria (randomized control studies) and three studies met level 2 criteria (non-randomized controlled trials). This translates into level 1 evidence for 14 GTS patients, level 2 evidence for 38 patients, and level 4 evidence for 36 patients. The authors concluded that in light of the wide spectrum of associated behavioral co-morbidities in GTS, multiple networks modulation may result in the most efficacious treatment strategy. The optimal locations for DBS within the cortico-basal ganglia-thalamocortical circuits remain to be established. However, at the current stage, comparison between targets should be done with great caution. Significant differences between number of patients treated per target, methodological variability, and quality of reporting makes a meaningful comparison between targets difficult. According to the authors, randomized controlled trials with larger cohorts and standardization of procedures are needed.

Porta et al. (2012) assessed the long term (5-6 years) outcome of bilateral thalamic deep brain stimulation in 18 patients with severe and refractory Tourette syndrome. The aim of the research was the assessment of long-term outcome on tics, obsessional behaviors, anxiety, mood, and on the overall general health of the patients and their general satisfaction. At 5-6 year follow-up, there was a significant reduction in tic severity, and significant improvements in obsessive compulsive behaviors, anxiety and depressive symptoms. Patients, in general, required less medication for tics, co-morbid conditions and/or co-existent psychopathologies. The long-term outcome and satisfaction were not unanimous between patients and the medical team. According to the authors, at long-term follow-up, DBS was very successful in terms of a significant improvement in tics and also a significant reduction in the potentially disabling symptoms of obsessionality, anxiety and depression. However, compared with the more positive overall results at 2 years, these later results demonstrate long-term difficulties as follows: non-compliance, long-term complications, and the differences in the opinions between the medical, the surgical teams and the post-DBS patients as to their outcome/satisfaction with the procedures. The authors indicated that this emphasizes the need for controlled studies, for long-term follow up, and the need to improve the selection of patients for DBS.

Steeves et al. (2012) conducted a systematic literature search for clinical trials on the treatment of tics. Three studies on deep brain stimulation (DBS) met the inclusion criteria. According to the authors, although evidence exists for the efficacy of DBS, the quality of this evidence is poor and the risks and burdens of the procedure are finely balanced with the perceived benefits. The author recommended that this intervention continues to be considered an experimental treatment for severe, medically refractory tics that have imposed severe limitations on quality of life. According to the authors, the procedure should only be performed within the context of research studies and by physicians who are expert in DBS programming and in the management of tics.

Sachdev et al. (2014) evaluated 17 patients who underwent deep brain stimulation (DBS) of the antero-medial globus pallidus interna (GPi) for severe Tourette Syndrome (TS). Follow up was at one month, three months and finally at a mean 24.1 months (range 8-46 months) following surgery. Overall, there was a 48.3% reduction in motor tics and a 41.3% reduction in phonic tics
at one month, and this improvement was maintained at final follow-up. 12 out of 17 (70.6%) patients had a>50% reduction in YGTSS score at final follow-up. Only 8 patients required ongoing pharmacotherapy for tics post-surgery. Patients improved significantly on all secondary measures. Adverse consequences included lead breakage in 4 patients, infection (1), transient anxiety (2), dizziness (1), poor balance (1) and worsening of stuttering (1). The authors concluded that this case series provides further support that antero-medial GPi DBS is an effective and well tolerated treatment for a subgroup of severe TS, with benefits sustained up to 4 years. This is an uncontrolled study with a small sample size.

Okun et al. (2013) performed a small National Institutes of Health-sponsored clinical trials planning study of the safety and preliminary efficacy of implanted DBS in the bilateral centromedian thalamic region for Tourette syndrome in 5 patients. The study used a cranially contained constant-current device and a scheduled, rather than the classic continuous, DBS paradigm. Baseline vs 6-month outcomes were collected and analyzed. In addition, the study compared acute scheduled vs acute continuous vs off DBS. Baseline vs 6-month data revealed that reductions in the Yale Global Tic Severity Scale (YGTSS) total score did not achieve the pre-study criterion of a 50% improvement in the YGTSS total score on scheduled stimulation settings. However, statistically significant improvements were observed in the YGTSS total score, impairment score, and motor score, the Modified Rush Tic Rating Scale Score total score; and the phonic tic severity score. Continuous, off, and scheduled stimulation conditions were assessed blindly in an acute experiment at 6 months after implantation. The scores in all 3 conditions showed a trend for improvement. Trends for improvement also occurred with continuous and scheduled conditions performing better than the off condition. Tic suppression was commonly seen at ventral (deep) contacts, and programming settings resulting in tic suppression were commonly associated with a subjective feeling of calmness. The authors concluded that this study provides safety and proof of concept that a scheduled DBS approach could improve motor and vocal tics in Tourette syndrome. Refinements in neurostimulator battery life, outcome measure selection, and flexibility in programming settings can be used to enhance outcomes in a future larger study. According to the authors, scheduled stimulation holds promise as a potential first step for shifting movement and neuropsychiatric disorders toward more responsive neuromodulation approaches.

A European guideline on DBS was developed by a working group of the European Society for the Study of Tourette Syndrome (ESSTS). A systematic literature search was conducted and expert opinions of the guidelines group contributed also to the recommendations. Of 63 patients reported so far in the literature, 59 had a beneficial outcome following DBS with moderate to marked tic improvement. However, randomized controlled studies including a larger number of patients are still lacking. Although persistent serious adverse effects (AEs) have hardly been reported, surgery-related (e.g., bleeding, infection) as well as stimulation-related AEs (e.g., sedation, anxiety, altered mood, changes in sexual function) may occur. According to the ESSTS working group, at the present time, DBS in TS is still in its infancy. Due to both different legality and practical facilities in different European countries these guidelines, therefore, need to be understood as recommendations of experts. However, among the ESSTS working group on DBS in TS there is general agreement that, at present time, DBS should only be used in adult, treatment resistant, and severely affected patients. It is highly recommended to perform DBS in the context of controlled trials (Müller-Vahl et al. 2011).

**Chronic Pain**

Bittar et al. (2005) performed a meta-analysis of DBS for pain relief that included 6 studies (n = 424 patients) published from 1977-1997. DBS was more effective for nociceptive than deafferentation pain (63% vs 47% long-term success). Long-term success was attained in over 80% of patients with intractable low back pain (failed back surgery) following successful trial stimulation. Trial stimulation was successful in approximately 50% of those with post-stroke pain, and 58% of patients permanently implanted achieved ongoing pain relief. Higher rates of success were seen with phantom limb pain and neuropathies. The authors concluded that DBS is frequently effective when used in well-selected patients. Neuroimaging and neuromodulation technology advances complicate the application of these results to modern practice.
Jung et al. (2015) evaluated the long-term effect of subthalamic nucleus deep brain stimulation (STN DBS) on pain in Parkinson disease (PD). Twenty-four patients who underwent STN DBS were studied. The assessments of pain were performed preoperatively and 8 years after surgery. Because 13 of the total 24 patients had additional 2-year postoperative data, the serial change between the preoperative and the 2- and 8-year follow-ups after surgery was also evaluated. Sixteen of the 24 patients (67%) experienced pain at baseline when not taking medication (off-state). All off-state pain at baseline improved or disappeared at 8 years after surgery. The number of body parts with pain was 21 at baseline and decreased to 11 at 8 years after the surgery. The mean (SD) and median scores of the off-state pain were 6.2 (2.5) and 7.0 at baseline and improved to 3.5 (2.2) and 2.5 at 8 years after the surgery, respectively. However, new pain developed in 18 of 24 patients (75%) during the 8-year follow-up period. The number of body parts with newly developed pain was 47. The types of new pain at 8 years were musculoskeletal in 11 patients, central in 4 patients, radiculoneuritic in 3 patients, and dystonic in 1 patient. Pain associated with PD is improved by STN DBS, and the beneficial effect persists after a long-term follow-up of 8 years. However, new pain, especially the musculoskeletal type, developed in most patients, becoming a long-term distressing problem.

In a National Institute for Health and Care Excellence (NICE) Guidance for refractory chronic pain syndromes (excluding headache), NICE stated that current evidence on the safety of deep brain stimulation for refractory chronic pain syndromes (excluding headache) shows that there are serious but well-known risks. There is evidence that the procedure is efficacious in some patients who are refractory to other forms of pain control. Therefore, NICE recommends that this procedure may be used provided that normal arrangements are in place for clinical governance, consent and audit (NICE 2011).

**Trigeminal Autonomic Cephalalgias**

In a National Institute for Health and Care Excellence (NICE) Guidance for deep brain stimulation for intractable trigeminal autonomic cephalalgias, NICE stated that current evidence on the efficacy of deep brain stimulation for intractable trigeminal autonomic cephalalgias (TACs) is limited and inconsistent, and the evidence on safety shows that there are serious but well-known side effects. Therefore, NICE recommends that this procedure should only be used with special arrangements for clinical governance, consent and audit or research (NICE 2011).

The clinical evidence was reviewed in October 2015 with no additional information identified that would change the conclusion for trigeminal autonomic cephalalgias.

**Cluster Headache**

Fontaine et al. (2010) performed a prospective crossover, double-blind, multicenter study assessing the efficacy and safety of unilateral hypothalamic DBS in 11 patients with severe refractory chronic cluster headache (CCH). The randomized phase compared active and sham stimulation during 1-month periods, and was followed by a 1-year open phase. During the randomized phase, no significant change in primary and secondary outcome measures was observed between active and sham stimulation. At the end of the open phase, 6/11 patients responded to the chronic stimulation (weekly frequency of attacks decreased by at least 50%), including three pain-free patients. There were three serious adverse events, including subcutaneous infection, transient loss of consciousness and micturition syncopes. According to the investigators, randomized phase findings of this study did not support the efficacy of DBS in refractory CCH, but open phase findings suggested long-term efficacy in more than 50% patients, confirming previous data. Discrepancy between these findings justifies additional controlled studies.

The clinical evidence was reviewed in October 2015 with no additional information identified that would change the conclusion for cluster headache.

**Depression**

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

Morishita et al. (2014) performed a systematic review of the literature pertaining to DBS for treatment-resistant depression to evaluate the safety and efficacy of this procedure. The reviewers identified 22 clinical research papers with 5 unique DBS approaches using different targets, including nucleus accumbens, ventral striatum/ventral capsule, subgenual cingulate cortex, lateral habenula, inferior thalamic nucleus, and medial forebrain bundle. Among the 22 published studies, only 3 were controlled trials, and 2, as yet unpublished, multicenter, randomized, controlled trials evaluating the efficacy of subgenual cingulate cortex and ventral striatum/ventral capsule DBS were recently discontinued owing to inefficacy based on futility analyses. Overall, the published response rate to DBS therapy, defined as the percentage of patients with > 50% improvement on the Hamilton Depression Rating Scale, is reported to be 40-70%, and outcomes were comparable across studies. The authors concluded that DBS for MDD shows promise, but remains experimental and further accumulation of data is warranted.

Blomstedt et al. (2011) conducted a review of the literature on DBS in the treatment of major depressive disorder (MDD). According to the authors, the results of DBS in MDD have been presented in 2 case reports and 3 studies of 47 patients operated upon in 5 different target areas. Positive effects were presented in all studies and side effects have been minor. DBS in the nucleus accumbens resulted in a mean reduction of Hamilton depression rating scale (HDRS) of 36% after 1 year and 30% of the 10 patients achieved remission. DBS in the internal capsule/ventral striatum resulted in a reduction of 44% after 1 year, and at the last evaluation after in mean 2 years, 40% of the 15 patients were in remission. The 20 patients with subcallosal cingulated gyrus DBS had a reduction of HDRS of 52% after 1 year, and 35% were within 1 point from remission or in remission. The authors concluded that DBS is a promising treatment for therapy-refractory MDD. However, the authors also stated that the published experience is limited, and the method is at present an experimental therapy.

Smith (2014) conducted an exploratory meta-analysis to address deep brain stimulation for treatment of major depressive disorder. Data on benefits of deep brain electrical stimulation came from a recent review. Expert opinion plus random number software was used to generate hypothetical values for sham responding. An effect size of 1.71 was obtained for deep brain stimulation versus sham treatment in patients suffering from long-term treatment-resistant depression. The authors concluded that preliminary findings on deep brain electrical stimulation suggest that the procedure may be 71% more effective than sham treatment. Expressing these findings as patients-needed-to-treat, deep brain electrical stimulation is required by 2.9 patients with long-term treatment-resistant depression in order for one of them to benefit.

Dougherty et al. (2015) evaluated 30 patients with treatment-resistant depression who participated in a sham randomized controlled trial of deep brain stimulation (DBS). Patients were randomized to active versus sham DBS treatment in a blinded fashion for 16 weeks, followed by an open-label continuation phase. The primary outcome measure was response, defined as a 50% or greater improvement on the Montgomery-Åsberg Depression Rating Scale from baseline. There was no significant difference in response rates between the active (3 of 15 subjects; 20%) and control (2 of 14 subjects; 14.3%) treatment arms and no significant difference between change in Montgomery-Åsberg Depression Rating Scale scores as a continuous measure upon
completion of the 16-week controlled phase of the trial. According to the authors, future studies utilizing alternative study designs and stimulation parameters are needed.

Bewernick et al. (2012) reported the results of long-term follow-up of Deep brain stimulation (DBS) to the nucleus accumbens (NAcc-DBS). Results of long-term follow-up of up to 4 years of NAcc-DBS are described in a group of 11 patients: 12 months (n=11), 24 months (n=10), and last follow-up (maximum 4 years, n=5). Analyses were performed in an intent-to-treat method with last observation carried forward, thus 11 patients contributed to each point in time. In all, 5 of 11 patients (45%) were classified as responders after 12 months and remained sustained responders without worsening of symptoms until last follow-up after 4 years. Both ratings of depression and anxiety were significantly reduced in the sample as a whole from first month of NAcc-DBS on. All patients improved in quality of life (QoL) measures. One non-responder committed suicide. No severe adverse events related to parameter change were reported. The authors concluded that first-time preliminary long-term data on NAcc-DBS have demonstrated a stable antidepressant and anxiolytic effect and an amelioration of QoL in this small sample of patients suffering from TRD. None of the responders of first year relapsed during the observational period (up to 4 years). This study is limited by a small patient population and lack of a controlled comparator group.

A Comparative Effectiveness Review was prepared for the Agency for Healthcare Research and Quality (AHRQ) on Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults. The report indicated that clinical trial data on some of the developing nonpharmacologic interventions, such as deep brain stimulation were insufficient (from the published literature) to include them in the report. The authors stated that as the evidence bases grow to support the efficacy of such nonpharmacologic interventions, the newer strategies should be included in comparative effectiveness study designs (Gaynes et al. 2011).

Professional Societies
The Canadian Psychiatric Association and the Canadian Network for Mood and Anxiety Treatments (CANMAT):
In 2008-2009, the Canadian Psychiatric Association and the CANMAT partnered to produce evidence-based clinical guidelines for the treatment of depressive disorders. Among the four forms of neurostimulation for depression reviewed in the guidelines, electroconvulsive therapy (ECT) had the most extensive evidence, spanning seven decades. The investigators indicated that deep brain stimulation remains an investigational treatment (Kennedy, 2009).

The American Psychiatric Association (APA):
In a clinical practice guideline for the treatment of patients with major depressive disorder, the APA states that electroconvulsive therapy remains the treatment of best established efficacy against which other stimulation treatments (e.g., VNS, deep brain stimulation, transcranial magnetic stimulation, other electromagnetic stimulation therapies) should be compared. The APA did not assign a rating for the use deep brain stimulation in treating depression (Gelenberg et al. 2010).

Epilepsy
In a Cochrane review, Sprengers et al. (2014) assessed the efficacy, safety and tolerability of deep brain and cortical stimulation for refractory epilepsy based on randomized controlled trials (RCTs). Ten RCTs comparing one to three months of intracranial neurostimulation to sham stimulation were identified. One trial was on anterior thalamic DBS (n = 109); two trials on centromedian thalamic DBS (n = 20), but only one of the trials (n = 7; 14 treatment periods) reported sufficient information for inclusion in the quantitative meta-analysis; three trials on cerebellar stimulation (n = 22); three trials on hippocampal DBS (n = 15); and one trial on responsive ictal onset zone stimulation (n = 191). Evidence of selective reporting was present in four trials and the possibility of a carryover effect complicating interpretation of the results could not be excluded in 4 cross-over trials without any washout period. Moderate-quality evidence could not demonstrate statistically or clinically significant changes in the proportion of patients who were seizure-free or experienced a 50% or greater reduction in seizure frequency (primary outcome measures) after 1 to 3 months of anterior thalamic DBS in (multi)focal epilepsy,
responsive ictal onset zone stimulation in (multi)focal epilepsy patients and hippocampal DBS in (medial) temporal lobe epilepsy. However, a statistically significant reduction in seizure frequency was found for anterior thalamic DBS, responsive ictal onset zone stimulation and hippocampal DBS. Both anterior thalamic DBS and responsive ictal onset zone stimulation do not have a clinically meaningful impact on quality life after three months of stimulation (high-quality evidence). The authors concluded that only short term RCTs on intracranial neurostimulation for epilepsy are available. Compared to sham stimulation, one to three months of anterior thalamic DBS (multi)focal epilepsy, responsive ictal onset zone stimulation (multi)focal epilepsy and hippocampal DBS (temporal lobe epilepsy) moderately reduce seizure frequency in refractory epilepsy patients. Anterior thalamic DBS is associated with higher rates of self-reported depression and subjective memory impairment. SUDEP rates require careful monitoring in patients undergoing responsive ictal onset zone stimulation. The authors stated that there is insufficient evidence to make firm conclusive statements on the efficacy and safety of hippocampal DBS, centromedian thalamic DBS and cerebellar stimulation. According to the authors, there is a need for more, large and well-designed RCTs to validate and optimize the efficacy and safety of invasive intracranial neurostimulation treatments for epilepsy.

In a National Institute for Health and Care Excellence (NICE) Guidance for deep brain stimulation for refractory epilepsy, NICE stated that the evidence on the efficacy of deep brain stimulation for refractory epilepsy is limited in both quantity and quality. NICE recommends that this procedure should only be used with special arrangements for clinical governance, consent and audit or research (NICE 2012).

**The clinical evidence was reviewed in October 2015 with no additional information identified that would change the conclusion for epilepsy.**

**Obsessive Compulsive Disorder (OCD)**

Alonso et al. (2015) evaluated the efficacy and tolerability of deep brain stimulation (DBS) in obsessive-compulsive disorder (OCD) and the existence of clinical predictors of response using meta-analysis. Thirty-one studies involving 116 subjects were identified in a literature search. Global percentage of Yale-Brown Obsessive Compulsive Scale (Y-BOCS) reduction was estimated at 45.1% and global percentage of responders at 60.0%. Better response was associated with older age at OCD onset and presence of sexual/religious obsessions and compulsions. No significant differences were detected in efficacy between targets. Five patients dropped out, but adverse effects were generally reported as mild, transient and reversible. The authors concluded that their analysis confirms that DBS constitutes a valid alternative to lesional surgery for severe, therapy-refractory OCD patients. According to the authors, well-controlled, randomized studies with larger samples are needed to establish the optimal targeting and stimulation conditions and to extend the analysis of clinical predictors of outcome.

Hamani et al. (2014) conducted a systematic review of the literature and developed evidence-based guidelines on DBS for OCD that was sponsored by the American Society for Stereotactic and Functional Neurosurgery and the Congress of Neurological Surgeons (CNS) and endorsed by the CNS and American Association of Neurological Surgeons. Of 353 articles identified, 7 were retrieved for full-text review and analysis. The quality of the articles was assigned to each study and the strength of recommendation graded according to the guidelines development methodology of the American Association of Neurological Surgeons/Congress of Neurological Surgeons Joint Guidelines Committee. Of the 7 studies, 1 class I and 2 class II double-blind, randomized, controlled trials reported that bilateral DBS is more effective in improving OCD symptoms than sham treatment. The authors concluded that based on the data published in the literature, the following recommendations can be made: (1) There is Level I evidence, based on a single class I study, for the use of bilateral subthalamic nucleus DBS for the treatment of medically refractory OCD. (2) There is Level II evidence, based on a single class II study, for the use of bilateral nucleus accumbens DBS for the treatment of medically refractory OCD. (3) There is insufficient evidence to make a recommendation for the use of unilateral DBS for the treatment of medically refractory OCD. The authors noted that additional research is needed to determine which patients respond to deep brain stimulation and if specific targets may be more suitable to treat a specific set of symptoms.
Kisely et al. (2014) conducted a systematic review and meta-analysis of double-blind, randomized controlled trials (RCTs) of active versus sham treatment to evaluate the effectiveness of DBS for psychiatric conditions. Inclusion criteria were met by five studies, all of which were for OCD. Forty-four subjects provided data for the meta-analysis. The main outcome was a reduction in obsessive symptoms as measured by the Yale-Brown Obsessive Compulsive Scale (YBOCS). Patients on active, as opposed to sham, treatment had a significantly lower mean score representing partial remission. However, one-third of patients experienced significant adverse effects (n = 16). There were no differences between the two groups in terms of other outcomes. The authors concluded that DBS may show promise for treatment-resistant OCD but there are insufficient randomized controlled data for other psychiatric conditions. According to the authors, DBS remains an experimental treatment in adults for severe, medically refractory conditions until further data are available.

**Professional Societies**

American Psychiatric Association (APA): In a Guideline Watch Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder, the APA states that new studies are available on deep brain stimulation (DBS) and other somatic treatments, but the overall strength of evidence for these treatments remains low (APA, 2013).

**Other Disorders**

Deep brain stimulation (DBS) has also been investigated for other disorders including Alzheimer's disease (Laxton, 2010; Smith, 2012; Hardenacke et al., 2013), impulsive or violent behavior (Franzini, 2005), and movement disorders of multiple sclerosis. (Hosseini, 2012; Hyam, 2007; Thevathasan, 2011; Mandat, 2010)

Studies investigating DBS for treatment of other conditions are mainly case series with small sample sizes and short-term follow-up. Further well-designed studies are needed to demonstrate the benefits of deep brain stimulation for these disorders.

**U.S. FOOD AND DRUG ADMINISTRATION (FDA)**

Deep brain stimulation is a procedure and, therefore, not subject to FDA regulation. However, any medical devices, drugs, and/or tests used as part of this procedure may require FDA regulation.

**Parkinson’s Disease and Essential Tremor**

The FDA approved the Activa® Tremor Control System (Medtronic) on July 31, 1997. The device is indicated for unilateral thalamic stimulation for the suppression of tremor in the upper extremity in patients who are diagnosed with essential tremor or Parkinsonian tremor not adequately controlled by medications and where the tremor constitutes a significant functional disability. Available at: [http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm083894.htm](http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm083894.htm). Accessed October 12, 2015.

A January 14, 2002 Premarket Approval (PMA) supplement expanded use to include bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) as an adjunctive therapy in reducing some of the symptoms of advanced, levodopa-responsive Parkinson’s disease that are not adequately controlled with medication. Available at: [http://www.accessdata.fda.gov/cdrh_docs/pdf/P960009S007b.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf/P960009S007b.pdf). Accessed October 12, 2015.

On June 12, 2015, the FDA approved the Brio Neurostimulation System (St. Jude Medical), an implantable deep brain stimulation device intended to help reduce the symptoms of Parkinson’s disease and essential tremor. See the following Web site for more information: [http://www.accessdata.fda.gov/cdrh_docs/pdf14/P140009a.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf14/P140009a.pdf). Accessed October 7, 2015.
Dystonia
On April 15, 2003, the Activa® Dystonia Therapy System (Medtronic) received a Humanitarian Device Exemption (HDE) from the FDA for unilateral and bilateral stimulation of the internal globus pallidus or the subthalamic nucleus and is indicated as an aid in the treatment of chronic, intractable (drug refractory), primary dystonia, including generalized and segmental dystonia, hemidystonia and cervical dystonia. Activa Dystonia Therapy is limited to use in implanting centers that receive Institutional Review Board (IRB) approval for the procedure. The safety and effectiveness of Activa Dystonia Therapy have not been established through a full PMA study. The therapy is approved for patients who are seven years of age and older. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpm/pma.cfm?num=H020007. Accessed October 12, 2015.

Obsessive Compulsive Disorder
On March 28, 2005, the Activa® Deep Brain Stimulation Therapy System was designated as a Humanitarian Use Device (HUD) for the treatment of chronic, treatment-resistant obsessive compulsive disorder (OCD) in a subset of patients. However, the FDA does not list a Humanitarian Device Exemption (HDE) approval for authorization to market the device.

On February 19, 2009, the Reclaim™ Deep Brain Stimulation Therapy device was designated as an HUD for the treatment of obsessive compulsive disorder (OCD). This device is indicated for bilateral stimulation of the anterior limb of the internal capsule (AIC) as an adjunct to medications and as an alternative to anterior capsulotomy for treatment of chronic, severe, treatment-resistant OCD in adult patients who have failed at least three selective serotonin reuptake inhibitors (SSRIs). See the following Web site for more information: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpm/pma.cfm?num=H050003. Accessed October 12, 2015.

Epilepsy
The Medtronic DBS therapy for refractory epilepsy (also known as the Intercept™ Epilepsy Control System) is under review by the FDA. On March 12, 2010, the FDA Neurological Devices Panel voted seven to five to recommend approval with conditions for the Medtronic DBS System for Epilepsy, and a final decision from FDA is pending. Medtronic submitted a premarket approval application (PMA) supplement in July 2009 for the Medtronic DBS System for Epilepsy as adjunctive treatment for partial-onset seizures in adults with medically refractory (i.e., treatment-resistant) epilepsy. Results from the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) trial supported Medtronic’s PMA. With the exception of the Intercept Patient Programmer, all components of the Medtronic system currently have U.S. marketing approval for other DBS indications as part of the Medtronic Activa PC Neurostimulation System for Tremor Control and Parkinson’s disease. The panel recommended the following conditions of approval for epilepsy:

- Labeling changes to address the increased risk of adverse events, including suicidal thoughts and actions, depression, memory problems, anxiety, and stimulation-related increased seizure frequency
- A five-year post-approval study that is hypothesis-driven, that has a control group, and targets various subgroups not well-defined in previous trials and that includes input from psychiatric experts to create an appropriate screening tool for suicidal tendencies


Additional Products
Activa® Tremor Control Therapy (Medtronic, Inc.)
Activa® Parkinson’s Control Therapy (Medtronic, Inc.)
Activa® Dystonia Therapy (Medtronic, Inc.)
Intercept™ Epilepsy Control System
REFERENCES

The foregoing Oxford policy has been adapted from an existing UnitedHealthcare national policy that was researched, developed and approved by UnitedHealthcare Medical Technology Assessment Committee. [2016T0321Q]


### POLICY HISTORY/REVISION INFORMATION

<table>
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<th>Date</th>
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| 03/01/2016 | - Updated list of applicable CPT codes; removed notation pertaining to Medical Director review/precertification requirements  
- Updated supporting information to reflect the most current clinical evidence, FDA information and references  
- Archived previous policy version SURGERY 090.13 T2 |