

Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1701 – Deep brain stimulation of the thalamus for the treatment of severe refractory epilepsy

Applicant: Neurosurgical Society of Australasia

Date of MSAC consideration: 30-31 March 2023

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of deep brain stimulation (DBS) of the thalamus for the management of severe treatment refractory epilepsy was received from the Neurosurgical Society of Australasia by the Department of Health and Aged Care.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC did not support the public funding of deep brain stimulation (DBS) of the anterior thalamus for the treatment of patients with severe treatment refractory epilepsy. MSAC noted the limitations of the evidence, such as the age of the evidence (implant surgery ranging from pre-1993 to 2015), the high drop-out rate in the pivotal trial, limited patient relevant outcomes, and the lack of long-term comparative safety and effectiveness data. MSAC considered that DBS was non-inferior in effectiveness and inferior in safety relative to both comparators, vagus nerve stimulation (VNS) and optimised medical therapy (OMT). MSAC noted the potential for DBS to cause further harm without clear benefit in patients who already experience a high level of disease burden. MSAC considered the economic model was driven by the time horizon that had a reducing incremental cost-effectiveness ratio (ICER) over longer time horizons but was unsupported by evidence beyond 3 months. MSAC noted the higher cost of the DBS device compared to VNS and OMT but considered the financial impact to be modest due to the small population and low risk of leakage. MSAC considered that further evidence of quality-of-life benefits for patients is needed, as well as a clearer definition of Comprehensive Epilepsy Program (CEP) referral centres.

Consumer summary

This is an application from the Neurological Society of Australasia requesting Medicare Benefits Schedule (MBS) listing of deep brain stimulation of the thalamus for the management of severe treatment refractory epilepsy.

Epilepsy is a condition where the person has epileptic seizures that are characterised by abnormal electrical activity in the brain, which can cause sudden and unpredictable changes in behaviour, movement and awareness. How the seizure affects a person depends on the area of the brain affected and how long the seizure lasts. There are many different underlying causes of epilepsy, including brain abnormalities present at birth, brain lesions that have developed during

Consumer summary

a person's lifetime and genetic causes. "Severe treatment refractory epilepsy" for the purpose of this application, describes a condition where almost all available treatment options have been attempted (such as medications or surgery) to reduce the frequency and intensity of seizures with little to no benefit.

Deep brain stimulation delivers electrical impulses to a key central location deep in the brain, called the thalamus, suppressing abnormal electrical activity within the brain that causes seizures. Under general anaesthetic, a neurosurgeon places electrode leads into the thalamus through small holes in the skull. The leads are connected to wires running under the skin behind the ear and down the side of the neck and are attached to a battery-powered device implanted in the upper chest. The device delivers electrical impulses to the brain. After the device is implanted, the electrical impulses delivered by the device are adjusted, with the aim of reducing how often seizures occur and how severe they are.

MSAC compared deep brain stimulation to two other common treatments, which are vagus nerve stimulation and optimised medical therapy (medications). Vagus nerve stimulation is similar to deep brain stimulation and also involves the implantation of a device in the chest and electrode leads to deliver electrical impulses and reduce the frequency and severity of seizures. The main difference is that in vagus nerve stimulation the leads are connected to the vagus nerve, which is found in the neck, rather than requiring brain surgery to place the electrodes.

MSAC considered that there was an insufficient amount of evidence presented to confidently support the safety and effectiveness claims of deep brain stimulation in epilepsy. MSAC considered there were issues with the presented evidence such as; the main study did not compare deep brain stimulation and vagus nerve stimulation for a long enough time, the number of patients that stopped participating in the main study was very high and all the studies were relatively old (they had been completed at least 7 years ago or more). MSAC were also concerned about the insufficient amount of reporting in the studies on outcomes and benefits that are valued by patients (e.g. a difference measured on a test could be considered a benefit by a doctor, but a patient may not notice any difference or improvement in their day-to-day life). MSAC considered that deep brain stimulation was not as safe and did not work better than the two other treatment options it was being compared to.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC did not support the public funding of deep brain stimulation of the thalamus for the treatment of patients with severe treatment refractory epilepsy. MSAC noted that the evidence was relatively old and that there was not enough long-term data relating to the safety and effectiveness of deep brain stimulation in epilepsy.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this was an application from the Neurological Society of Australasia requesting Medicare Benefits Schedule (MBS) listing of deep brain stimulation (DBS) of the anterior thalamus for the management of severe treatment refractory epilepsy. MSAC noted the application sought to add this indication to existing MBS listings for DBS in the treatment of Parkinson's disease, essential tremor and dystonia. MSAC noted there are very few patients with this condition, but they experience a high burden of disease and the overall aim of undergoing DBS is to manage the condition better by reducing the frequency and severity of epileptic seizures and thereby improving quality-of-life (QoL) for the patient.

MSAC noted ESC advice that the therapy should be restricted to focal epilepsy based on the current available evidence. During the evaluation, severe treatment refractory epilepsy was used to describe where a patient's condition had become treatment refractory (and not just drug refractory). Drug refractory was defined as a patient who continued to experience seizures despite the use of 2 or more antiepileptic medications (referred to as optimised medical therapy (OMT)) at therapeutic doses. MSAC noted that International League Against Epilepsy guidelines require drug refractory to be demonstrated by resistance to 2 antiepileptic medications¹. Eligible patients must also have been considered for curative resective brain surgery and be either deemed unsuitable or treated unsuccessfully. MSAC noted ESC's addition that patient refusal to consent to resective brain surgery should also be considered. Lastly, all eligible patients will have been referred to and assessed by a comprehensive epilepsy program (CEP), which is a 1–2-week inpatient program providing comprehensive assessment of patients with uncontrolled epilepsy.

MSAC considered that the small number of patients included in the studies, and the age of the studies, having been conducted between the early 1990s and 2015, limited the applicability and validity of the comparisons between DBS and VNS, given the improvements in both hardware design and clinical efficacy over the last decade. MSAC noted that none of the included studies directly compared DBS with OMT and only one small self-controlled case-series study (n=11) directly compared DBS with VNS but had a high risk of bias. MSAC noted the pivotal trial was the SANTE trial which compared DBS to sham DBS and was well-conducted with low risk of bias, but it had a high drop-out rate over an extended follow-up timeframe; the long-term retention of subjects in the study was 66% at the 7-year visit. VNS and OMT data from the PULSE trial were applied as an indirect comparison for DBS versus OMT. MSAC noted the available evidence was limited on the use of DBS in older patients and young adults, due to the average age of patients undergoing DBS in the studies ranging from 28 to 40 years. MSAC considered the item descriptor should limit the item to adults.

MSAC noted the studies only provided evidence on the effects of DBS in patients with focal seizures. In some cases, those with secondary generalised seizures were also included, but their results could not be disaggregated. MSAC noted the applicant presented recent evidence from the Australian ESTEL trial² to support DBS in treating patients who had generalised epilepsy however, ESC considered the trial was not relevant to the scope of this application as the trial population only encompassed patients with a specific neurological condition (Lennox-Gastaut syndrome) and the trial aimed to target the centro-median thalamus, not the anterior thalamus as specified in the ratified PICO population. MSAC also noted the trial did not report a significant difference in the patient reported outcomes between the study arms.

MSAC noted that an open-label randomised controlled trial (RCT) was concluded in November 2021³ that directly compared DBS and VNS, and that this trial may provide significant additional data to inform the question of whether DBS is more effective than VNS in the patient group relevant to this application. However, MSAC noted that it is unclear when these results will be published. MSAC also noted that forthcoming RCTs comparing DBS with OMT are unlikely.

¹ Kwan et al., 2010. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia*

² Dalic et al., DBS of Thalamic Centromedian Nucleus for Lennox-Gastaut Syndrome (ESTEL Trial). *Ann Neurol*. 2022.

³ <https://clinicaltrials.gov/ct2/show/NCT02076698>

MSAC did not agree with the applicant's clinical claim that DBS was superior in effectiveness and non-inferior in safety versus both comparators. MSAC considered DBS was inferior in safety relative to OMT and VNS, noting the more invasive nature of surgery required for implementation of DBS. MSAC also noted the SANTE trial reported a rate of serious device-related adverse events of 35% relating to DBS. MSAC considered the evidence base may overestimate the rates of device-related adverse events and underestimate the effectiveness associated with DBS and may not reflect the results achievable in current practice however, there is potential for DBS to cause further harm without clear benefit in patients who already experience a high level of disease burden.

MSAC considered that DBS was non-inferior in effectiveness compared to VNS. MSAC considered that DBS may potentially be superior compared to OMT, noting the SANTE trial reported a 17% reduction in frequency of seizures compared to sham DBS/OMT, but there was no change in seizure severity or QoL. MSAC considered there was no long-term direct comparative evidence presented to support this claim following the cross over period at 3 months. MSAC noted that 74% of patients remaining in the trial after 7 years had a median seizure frequency reduction of 50% but these results were confounded by the high drop-out rate in the non-responders. The pre-MSAC response argued that DBS response improves over time, but MSAC considered this was not clearly supported with confidence by the data presented. Overall, MSAC considered the potential benefit of DBS, even in circumstances where seizure frequency may be reduced, did not balance out the increased risk of adverse events. MSAC also considered there were limited QoL gains seen in the presented evidence for patients.

MSAC noted the economic evaluation was a cost-utility analysis, with extrapolated time horizons of 3 months, 7 years and lifetime. Outcomes measured were quality-adjusted life-years gained (QALYs) and change in seizure frequency. MSAC noted the incremental cost effectiveness ratios (ICERs) were high at \$1,625,659/QALY (3 months), \$381,796/QALY (7 years) and \$143,395/QALY (lifetime). MSAC considered the 7 year and lifetime time horizons were unsupported due to the limited evidence available from the SANTE trial with a follow up of 3 months. MSAC considered the lack of long-term comparative data beyond 3 months introduced uncertainties into the model where the ICERs were already considered to be high. MSAC noted that the cost of the device and hospital care, and the percentage of responders were also important drivers of the ICER. MSAC considered the model to be inappropriate because a cost-utility analysis is based on the assumption of clinical superiority, which MSAC did not accept.

MSAC noted the higher cost of the DBS device compared to VNS and OMT but considered the financial impact would potentially be modest due to the small population and low risk of leakage; a total of 30 patients are estimated to receive MBS supported DBS implementation in the first year, either as direct substitution for VNS or as an additional service. Net increase to the MBS was estimated to be \$159,556 in year 1 up to \$410,124 in year 6. MSAC considered that despite the low impact to the MBS, it would be a high cost for the utility gained with the current economic model. MSAC noted that uptake was limited by the need for CEP referral so the risk of leakage was low, however CEPs were not available in Tasmania, the Australian Capital Territory and the Northern Territory. MSAC considered that increase in CEP availability or capacity may increase the uptake of DBS for epilepsy and therefore increase the costs to the MBS. MSAC therefore considered that a clearer definition of CEP referral is needed prior to any implementation.

MSAC considered that further evidence to support improvements in QoL outcomes for patients is needed. MSAC considered the claim that DBS reduces seizure frequency and severity cannot reconcile the lack of patient (or carer) reported benefits. MSAC considered that more robust evidence is required to demonstrate that DBS offers a significant benefit in effectiveness versus the comparators to balance out the safety concerns.

4. Background

MSAC has not previously considered DBS of the thalamus for the treatment of severe refractory epilepsy in adults.

DBS is currently funded by MBS in Australia for the following indications:

- treatment of Parkinson's disease where the patient's response to medical therapy is not sustained and is accompanied by unacceptable motor fluctuations
- treatment of essential tremor or dystonia where the patient's symptoms cause severe disability.

MBS items 40851, 40852, 40854, 40856, 40858, 40860, 40862 for the above indications were introduced on the MBS from 1 November 2006.⁴

5. Prerequisites to implementation of any funding advice

There are no prerequisites to the implementation of DBS of the thalamus for the treatment of severe refractory epilepsy. It does not depend on approval of any therapeutic item by the TGA, noting there are ARTG listings for a DBS device and its associated components indicated for epilepsy (Percept™ PC), sponsored by Medtronic Australasia Pty Ltd (Table 1). In addition, there are various consumables that will be used as part of the service which are also listed on the ARTG, as described in Table 2.

Table 1 Components of the Percept PC, neurostimulator (Medtronic Australasia Pty Ltd) listed on the ARTG

Summary for ARTG entry	ARTG number
Percept PC BrainSense B35200 – Brain electrical stimulation system, antitremor	351630
Bur hole cover	151095
Electrode/lead, stimulator, implantable, neurological, model 3387	137374
Neural-tissue electrical stimulation lead adapter	239412
TH91D – Multi-purpose electrical stimulation system programmer	351590

Table 2 Consumables (all Medtronic Australasia Pty Ltd) associated with the DBS service that are listed on the ARTG

Summary for ARTG entry	ARTG number
Tunneller, ligament/tendon	121281
Electrode, electroencephalograph	133619
Cable/lead, electroencephalograph	138186
Stereotactic surgery system probe, single use	212222
Cable (twist lock)	119991
Cable (Alligator clip)	119991
Surgical procedure kit, neurosurgical, single use, non-medicated	240576

⁴ Australian Government Department of Health and Aged Care 2022, MBS Online, viewed October 11 2022, <<http://www9.health.gov.au/mbs/search.cfm>>.

6. Proposal for public funding

Funding is sought via the MBS by amending the patient population for existing MBS items (40851, 40852, 40854, 40856, 40858, 40860, 40862) for DBS. The proposed amendments to these existing MBS items are marked in blue italics in Table 3 through to Table 9.

The aim is to expand current MBS items for DBS to include adults with epilepsy who have been evaluated at a CEP and have been determined to have drug refractory epilepsy and who are not suitable for resective surgery or have undergone surgery unsuccessfully.

No changes have been proposed to the existing fees.

Table 3 Proposed amendment to MBS item 40851

Category 3 – THERAPEUTIC PROCEDURES
<p>MBS item 40851</p> <p>DEEP BRAIN STIMULATION (bilateral) functional stereotactic procedure including computer assisted anatomical localisation, physiological localisation including twist drill, burr hole craniotomy or craniectomy and insertion of electrodes for the treatment of:</p> <p>Parkinson's disease where the patient's response to medical therapy is not sustained and is accompanied by unacceptable motor fluctuations; or</p> <p>Essential tremor or dystonia where the patient's symptoms cause severe disability; or</p> <p><i>The anterior thalamus to treat people who are 18 years and older with drug-refractory focal epilepsy where resection of the brain is either contraindicated or refused by the patient, or if the patient has received resection of the brain but was unsuccessful in halting seizures, following assessment by a Comprehensive Epilepsy Program.</i></p> <p>Multiple Operation Rule (Anaes.) (Assist.)</p>
Fee: \$4,123.60 Benefit: 75% = \$3,092.70

Table 4 Proposed amendment to MBS item 40852

Category 3 – THERAPEUTIC PROCEDURES
<p>MBS item 40852</p> <p>Proposed item descriptor:</p> <p>DEEP BRAIN STIMULATION (unilateral) subcutaneous placement of neurostimulator receiver or pulse generator for the treatment of:</p> <p>Parkinson's disease where the patient's response to medical therapy is not sustained and is accompanied by unacceptable motor fluctuations; or</p> <p>Essential tremor or dystonia where the patient's symptoms cause severe disability; or</p> <p><i>The anterior thalamus to treat people who are 18 years and older with drug-refractory focal epilepsy where resection of the brain is either contraindicated or refused by the patient, or if the patient has received resection of the brain but was unsuccessful in halting seizures, following assessment by a Comprehensive Epilepsy Program.</i></p> <p>Multiple Operation Rule (Anaes.) (Assist.)</p>
Fee: \$354.40 Benefit: 75% = \$265.80

Table 5 Proposed amendment to MBS item 40854

Category 3 – THERAPEUTIC PROCEDURES
MBS item 40854 DEEP BRAIN STIMULATION (unilateral) revision or removal of brain electrode for the treatment of: Parkinson's disease where the patient's response to medical therapy is not sustained and is accompanied by unacceptable motor fluctuations; or Essential tremor or dystonia where the patient's symptoms cause severe disability; or <i>The anterior thalamus to treat people who are 18 years and older with drug-refractory focal epilepsy where resection of the brain is either contraindicated or refused by the patient, or if the patient has received resection of the brain but was unsuccessful in halting seizures, following assessment by a Comprehensive Epilepsy Program.</i>
Multiple Operation Rule (Anaes.) (Assist.)
Fee: \$547.70 Benefit: 75% = \$410.80

Table 6 Proposed amendment to MBS item 40856

Category 3 – THERAPEUTIC PROCEDURES
MBS item 40856 DEEP BRAIN STIMULATION (unilateral) removal or replacement of neurostimulator receiver or pulse generator for the treatment of: Parkinson's disease where the patient's response to medical therapy is not sustained and is accompanied by unacceptable motor fluctuations; or Essential tremor or dystonia where the patient's symptoms cause severe disability; or <i>The anterior thalamus to treat people who are 18 years and older with drug-refractory focal epilepsy where resection of the brain is either contraindicated or refused by the patient, or if the patient has received resection of the brain but was unsuccessful in halting seizures, following assessment by a Comprehensive Epilepsy Program.</i>
Multiple Operation Rule (Anaes.) (Assist.)
Fee: \$265.80 Benefit: 75% = \$199.35

Table 7 Proposed amendment to MBS item 40858

Category 3 – THERAPEUTIC PROCEDURES
MBS item 40858 DEEP BRAIN STIMULATION (unilateral) placement, removal or replacement of extension lead for the treatment of: Parkinson's disease where the patient's response to medical therapy is not sustained and is accompanied by unacceptable motor fluctuations; or Essential tremor or dystonia where the patient's symptoms cause severe disability; or <i>The anterior thalamus to treat people who are 18 years and older with drug-refractory focal epilepsy where resection of the brain is either contraindicated or refused by the patient, or if the patient has received resection of the brain but was unsuccessful in halting seizures, following assessment by a Comprehensive Epilepsy Program.</i>
Multiple Operation Rule (Anaes.) (Assist.)
Fee: \$547.70 Benefit: 75% = \$410.80

Table 8 Proposed amendment to MBS item 40860

Category 3 – THERAPEUTIC PROCEDURES
MBS item 40860 DEEP BRAIN STIMULATION (unilateral) target localisation incorporating anatomical and physiological techniques, including intraoperative clinical evaluation, for the insertion of a single neurostimulation wire for the treatment of: Parkinson's disease where the patient's response to medical therapy is not sustained and is accompanied by unacceptable motor fluctuations; or Essential tremor or dystonia where the patient's symptoms cause severe disability; or <i>The anterior thalamus to treat people who are 18 years and older with drug-refractory focal epilepsy where resection of the brain is either contraindicated or refused by the patient, or if the patient has received resection of the brain but was unsuccessful in halting seizures, following assessment by a Comprehensive Epilepsy Program.</i>
Multiple Operation Rule (Anaes.) (Assist.)
Fee: \$2,104.65 Benefit: 75% = \$1,578.50

Table 9 Proposed amendment to MBS item 40862

Category 3 – THERAPEUTIC PROCEDURES
MBS item 40862 DEEP BRAIN STIMULATION (unilateral) electronic analysis and programming of neurostimulator pulse generator for the treatment of: Parkinson's disease where the patient's response to medical therapy is not sustained and is accompanied by unacceptable motor fluctuations; or Essential tremor or dystonia where the patient's symptoms cause severe disability; or <i>The anterior thalamus to treat people who are 18 years and older with drug-refractory focal epilepsy where resection of the brain is either contraindicated or refused by the patient, or if the patient has received resection of the brain but was unsuccessful in halting seizures, following assessment by a Comprehensive Epilepsy Program.</i>
Multiple Operation Rule (Anaes.) (Assist.)
Fee: \$197.40 Benefit: 75% = \$148.05 85% = \$167.80

The delivery of DBS should be restricted to neurosurgeons in conjunction with neurologists. It is intended to be provided in an inpatient setting in public or private hospitals.

An issue with the proposed MBS item descriptor is that it did not specify which section of the brain should be treated by DBS for drug refractory epilepsy. In the ratified PICO, PASC confirmed that the proposed intervention is 'deep brain stimulation of the anterior nuclei of the anterior thalamus.' This might be important given other sections of the brain have been treated in studies on DBS for drug refractory epilepsy. In addition, the MBS item descriptor did not specify that the treatment should be limited to adults. Further, in the PICO, PASC confirmed that the application proposes an amendment to the eligible population for DBS 'to encompass people with drug refractory epilepsy where resection of the brain is either contraindicated or has been unsuccessful in halting seizures', whereas the descriptor only mentions patients not suitable for resective surgery.

It should be noted that there is also an MSAC application for DBS for treatment-refractory obsessive-compulsive disorder (application 1727) and this also proposes amendment to MBS items 40851, 40852, 40854, 40856, 40858, 40860, 40862 if listed.

7. Population

The target population is adult patients with drug refractory (focal or generalised) epilepsy who have been assessed by a CEP and deemed either ineligible for curative resective brain surgery or who have undergone surgery unsuccessfully.

Patients with drug refractory epilepsy are defined as those who fail to become (and stay) seizure-free with adequate trials of 2 AEMs at therapeutic levels¹. AEMs may be trialled sequentially or in conjunction with other AEMs. Approximately 30–40% of patients are diagnosed with drug refractory epilepsy after failed trials of AEMs.⁵

CEPs are 1–2-week inpatient programs providing comprehensive assessment of patients with uncontrolled epilepsy. In general, the program aims to determine the nature and type of the patient's episodes and whether surgical treatment may be suitable. Tests conducted during the program may include video electroencephalography (VEEG) monitoring, assessment by a neuropsychologist, assessment for mood disorders, neurosurgical assessment of the safety and feasibility of surgery, and neuroradiological investigations.⁶

Resective brain surgery involves the removal of the area of the brain where seizures occur. It is considered in patients with focal epilepsy where seizures originate from a region of the brain that can be removed with minimal risk of neurological or cognitive dysfunction.⁷ The expected outcome of resective brain surgery is seizure control with medication, which may be achieved in up to 70% of patients.⁸

DBS is proposed as a replacement or alternative therapy to VNS, which is currently MBS-funded for the same patient cohort. DBS may also be used in addition to VNS, as a new service to be delivered in the future after an unsuccessful trial of VNS.⁹

The decision to undergo neuromodulation (DBS or VNS) to treat drug refractory epilepsy is a complex one, requiring the expert opinion of qualified neurosurgeons and epilepsy neurologists practicing in a CEP. The decision is based on patient factors such as seizure type and epilepsy syndrome, neuroimaging features, electrographic characteristics and up-to-date knowledge of the literature.

Currently, the clinical management of people with drug refractory epilepsy involves referral to a CEP for evaluation. In patients who are ineligible for surgery, refuse surgery or have previously failed surgery, treatment options are VNS or continued AEM therapy. The addition of DBS to the clinical management algorithm means patients who are ineligible for surgery, refuse it or have previously failed surgery, have an additional treatment option and a second option is available in the case of failed VNS/DBS in the first instance.

⁵ Chen et al., 2018. Treatment Outcomes in Patients With Newly Diagnosed Epilepsy Treated With Established and New Antiepileptic Drugs: A 30-Year Longitudinal Cohort Study. *JAMA Neurology*

⁶ Australian Government Department of Health. 2022, Ratified PICO Confirmation - MSAC Application 1701 - Deep brain stimulation of the thalamus for the treatment of severe refractory epilepsy Medical Services Advisory Committee, Australia, <<http://msac.gov.au/internet/msac/publishing.nsf/Content/1701-public>>.

⁷ Miller et al., 2013. Surgical treatment of epilepsy. *Continuum (Minneapolis)*

⁸ Mayo Clinic. 2021, Epilepsy surgery. Patient Care & Health Information., viewed 27 September 2022, <<https://www.mayoclinic.org/tests-procedures/epilepsy-surgery/about/pac-20393981>>.

⁹ Australian Government Department of Health. 2022, Ratified PICO Confirmation - MSAC Application 1701 - Deep brain stimulation of the thalamus for the treatment of severe refractory epilepsy Medical Services Advisory Committee, Australia, <<http://msac.gov.au/internet/msac/publishing.nsf/Content/1701-public>>.

8. Comparator

The comparators to DBS of the thalamus for the treatment of severe refractory epilepsy are VNS and optimised medical treatment (OMT).

Similar to DBS, VNS is a neuromodulation treatment that is a palliative, non-pharmacological alternative and/or adjunct therapy for the management of seizures. It is not curative. It works by delivering mild pulses to the vagus nerve at regular intervals throughout the day via a small generator implanted in the chest and a lead attached to the vagus nerve in the neck¹⁰.

VNS first received regulatory approval in Australia in 2000 and was listed on the MBS in November 2017^{11 12}. The MBS descriptor for VNS is for (a) management of refractory generalised epilepsy, or (b) treatment of refractory focal epilepsy not suitable for resective epilepsy surgery. The MBS item numbers relating to VNS treatment for epilepsy are 40701, 40702, 40704, 40705, 40707 and 40708. VNS is provided in private and public hospitals in Australia.

OMT, or best supportive care, refers to individualised therapy judged optimal by a patient's treating physician. Since the target population is considered drug refractory, OMT often involves changes in antiepileptic drug type or dosage, or drug withdrawal.¹³

9. Summary of public consultation input

Consultation feedback was received from 2 professional organisations, 1 consumer organisation and 1 industry company that supplies medical devices such as those used for DBS:

- Epilepsy Foundation
- Epilepsy Society of Australia
- Movement Disorder Society of Australia and New Zealand (MDSANZ)
- Abbott Medical

The consultation feedback received was supportive of public funding for DBS of the thalamus for the treatment of drug refractory epilepsy.

Consultation feedback indicated the main benefits of public funding included:

- improved seizure control and increased patient independence, quality of life and employability
- reduced reliance on support services/family required
- reduced background antiepileptic medication dosing
- fewer side effects once immediate perioperative issues have settled, with benefits increasing over time
- reduced hospital admissions for recurrent seizures
- reduced carer stress.

¹⁰ Epilepsy Action Australia 2020, Vagus Nerve Stimulation (VNS), Epilepsy Action Australia, viewed 17 October 2022, <<https://www.epilepsy.org.au/about-epilepsy/managing-epilepsy/treatment/vagus-nerve-stimulation-vns/>>.

¹¹ Australian Government Department of Health and Aged Care 2022, MBS Online, viewed October 11 2022, <<http://www9.health.gov.au/mbs/search.cfm>>.

¹² The Royal Children's Hospital Melbourne 2022, Vagus nerve stimulation viewed October 11 2022, <https://www.rch.org.au/neurology/patient_information/vagus_nerve_stimulation/>.

¹³ Perucca et al., 2018. The management of epilepsy in children and adults. *Med J Aust*.

The consultation feedback noted that the main disadvantages related to:

- the invasive nature of the intervention,
- the associated risk of infection, and
- the need to replace the stimulator box for non-rechargeable devices.

The Epilepsy Foundation considered that DBS will improve the day-to-day lives of these patients, including increasing their independence, improving relationships with others and being less reliant on support services and family caring. They also considered that DBS as an available therapy for these patients will assist in reducing the overall cost of treatments and management of epilepsy to the health system.

10. Characteristics of the evidence base

The comparators specified in the PICO were VNS or OMT. However, none of the included studies compared DBS with OMT. Only one small self-controlled case-series study directly compared DBS with VNS. Since the comparator for the DBS studies was sham treatment (DBS turned off), studies comparing VNS with sham treatment were sought with the aim of finding a similar comparator arm that would enable a pairwise indirect comparison of DBS and VNS. However, sham VNS requires that the unit operates at a detectable but theoretically subtherapeutic level of stimulation. Therefore, neither DBS or VNS sham treatment is truly equivalent to OMT, nor are they similar enough to each other to use as a common comparator in a pairwise indirect comparison. Since there were no methodologically robust studies identified that directly compared DBS with the prespecified comparators in the PICO, the following approach was undertaken to synthesise the evidence:

- Data for DBS compared with OMT were derived from:
 - 2 randomised controlled trials (RCTs) directly comparing DBS with sham treatment (considered as a proxy for OMT)
 - ‘benchmark’ data for OMT derived from the control arm of one RCT
- Data for DBS compared with VNS were derived from:
 - one self-controlled case series study
 - ‘benchmark’ data derived from the intervention arms of 4 RCTs on VNS.

The key features of the included evidence are summarised in the table below.

Table 10 Key features of the included evidence

References	N	Design/duration	Risk of bias	Seizure type	Outcome(s)	Use in modelled evaluation
DBS versus sham DBS						
SANTE trial 2010	110	Double-blind RCT 3 months blinded phase (total FU = 10 years) ^a	Low	Focal, with or without secondary generalisation	<i>Effectiveness</i> Seizure frequency, seizure severity, quality of life <i>Safety</i> Adverse events, neuropsychological effects	Used
Herrman 2019	18	Double-blind RCT 6 months blinded phase (total FU = 12 months) ^a	Low	Focal, with or without secondary generalisation	<i>Effectiveness</i> Seizure frequency, seizure severity <i>Safety</i> Adverse events	Not used

References	N	Design/duration	Risk of bias	Seizure type	Outcome(s)	Use in modelled evaluation
DBS versus VNS (direct comparison)						
Kulju 2018	11 ^b	Self-controlled case series study ≥12 months	High	Focal and generalised	<i>Effectiveness</i> Seizure frequency	Not used
DBS versus VNS or OMT (indirect comparison)						
PuLsE Trial	112 ^c	Open label RCT ^d 12 months	Low	Focal	<i>Effectiveness</i> Seizure frequency, seizure severity, QoL <i>Safety</i> Adverse events, neuropsychological effects	Used
Amar 1998	17	Double-blind RCT ^d 3 months blinded phase (total FU = 18 months) ^a	Moderate	Complex focal, with or without secondary generalisation	<i>Effectiveness</i> Seizure frequency <i>Safety</i> Adverse events	Not used
Elger 2000	11	Double-blind RCT ^d 3 months blinded phase (total FU = 6 months) ^a	Moderate	Focal	<i>Effectiveness</i> Seizure frequency <i>Safety</i> Mood changes	Not used
Lamdy 1993	9	Double-blind RCT ^d 12–17 weeks blinded phase (extension 6–26 weeks; total length of FU unclear) ^a	Moderate	Complex focal seizures	<i>Effectiveness</i> Seizure frequency <i>Safety</i> Adverse events	Not used

Abbreviations: DBS = deep brain stimulation; FU = follow-up; OMT = optimised medical treatment; QoL = quality of life; RCT = randomised controlled trial; VNS = vagus nerve stimulation

Note: ^a All patients received therapeutic stimulation once the randomised, blinded phase of the trial concluded (case series data)

^b Included patients 17 years of age and older

^c Included patients 16 years of age and older

^d VNS and OMT arms were treated as separate datasets and, thus, were considered as case-series studies for this review

Limitations of the evidence base

The evidence base was limited not only by the small number of patients, but also the lack of direct comparisons between the interventions of interest. The limited duration of the blinded phases of the DBS trials also presents a challenge in interpreting the available comparative evidence because the extension results of these and other studies strongly suggest that the positive effects of DBS increase over time (often many months to years). Whether this cumulative effect also applies to the comparators is unclear.

The oldest patient included in the DBS studies was 61 years, with the average age of participants in each study ranging from 28 to 40 years. Thus, the available evidence provides no information on the use of DBS in older patients or young adults. In addition, all of the patients included in the

studies had focal seizures. In some cases those with secondary generalised seizures were also included but their results could not be disaggregated. Consequently, the studies only provide evidence on the effects of DBS in patients with focal epilepsy. It is unknown what proportion of Australians with severe drug refractory epilepsy fit this seizure profile.

An additional concern with respect to applicability is the age of the evidence base. The most recently conducted study completed the last DBS implant in 2015, while the VNS and other DBS studies reported on surgeries conducted at least a decade ago and, in some cases, nearly 3 decades ago. This severely limits the applicability and validity of the DBS and VNS comparisons, as significant improvements in both hardware design and clinical aspects have occurred since these studies were conducted. Thus, the assessed evidence base may overestimate the rates of device-related adverse events, underestimate the effectiveness associated with DBS and may not reflect the results achievable in current practice.

Forthcoming evidence

There are unlikely to be any large RCTs conducted to compare DBS with OMT in the near future. The SANTE trial is generally considered to be the seminal trial that proved the effectiveness of DBS in patients with drug refractory epilepsy, due to its quality, size and long length of follow-up. However, an open label RCT¹⁴, which began enrolling patients in 2014, has compared the safety, effectiveness and cost-effectiveness of DBS with VNS over two years in 62 patients with drug refractory focal or multifocal epilepsy with or without secondary generalised seizures (NCT02076698). The results of this trial, which was completed in November 2021, will provide additional data to inform the question of whether DBS is more effective than VNS in the patient group relevant to this assessment. However, there is currently no indication of when these results will be published.

11. Comparative safety

DBS versus sham DBS or OMT

Safety outcomes in the 2 RCTs (SANTE trial 2010 and Herrman 2019) were reported for each intervention arm during the double-blind phase as well as for the entire cohort once all patients started receiving active DBS (moderate quality evidence). The self-controlled case-series study did not report safety outcomes (Kulju 2018). It should be noted that in the 2 DBS RCTs surgical implantations occurred from December 2003 to March 2015, so the results may not reflect current DBS technology, surgical techniques and stimulation setting algorithms.

The rates of serious and non-serious treatment-related adverse events did not differ between groups in either RCT during the blinded phase. Serious device-related adverse events occurred in 35% of patients in the SANTE trial, the majority of which occurred in the first year after implantation. The most common of these in the operative phase were improper lead positioning (8%) and implant-site infection (4%).

While patients receiving active stimulation were more likely to report worsening of previously diagnosed or new onset depression (risk ratio [RR] 8.15, 95% confidence interval [CI] 1.05, 62.96) or memory impairment (RR 7.13, 95% CI 0.91, 56.02) during the blinded phase, this was not reflected in the objective measures for depression, anxiety and cognition. Most of these events were non-serious and often resolved over the long-term phase of the trial. Over the 7-year follow-

¹⁴ NCT02076698 - Deep Brain Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy (FRANCE). <<https://clinicaltrials.gov/ct2/show/NCT02076698>>

up period, there were no significant objective or subjective cognitive declines, neurobehavioral problems or affective distress relative to baseline in the 67 patients remaining in the study.

There were significantly fewer epilepsy-related injuries in the active stimulation group over the 3-month blinded period (RR 0.29, 95% CI 0.10, 0.83); none of the events were serious. There was no discernible difference between the 2 groups with respect to any other individual adverse events. After depression, memory impairment and epilepsy-related injuries, the most commonly reported complications were anxiety, dizziness and paraesthesia (tingling, shocking, vibration or a buzzing sensation).

Assessment of extended harms in the SANTE trial found that the most frequent device-related adverse events reported over the 7-year follow-up period were pain at the implant site (32%), paraesthesia (24%), device ineffectiveness (15%) and implant site infection (14%). During this time the device was removed permanently in just over a quarter of the patients, and half required neurostimulator replacement for battery depletion after 2.2 years. However, these data were collected from older devices implanted between 2003 and 2007. Current DBS stimulators have a projected battery life of more than 5 years, depending on the intensity and frequency of stimulation, and there are rechargeable stimulators now available that have a 15-year longevity.¹⁵

Even though the comparisons were head-to-head, sham DBS is a poor proxy for assessing the potential effects of OMT because the insertion of DBS electrodes into the brain can cause a lesion effect that has been shown to influence patient outcomes even when the unit is inactivated. It is unclear to what degree this, and the potential placebo effect of undergoing an invasive surgery, would confound outcomes related to medication alone. An indirect naïve comparison of DBS and OMT (low-quality evidence) indicated that those receiving DBS were 4 times more likely to experience an adverse event and 30 times more likely to have a serious adverse event.

DBS versus VNS (indirect naïve comparison)

Four of the included RCTs with therapeutic VNS treatment arms provided data on safety and effectiveness outcomes for a naïve indirect comparison with DBS. However, the VNS studies are unlikely to be representative of current practice, given that the most recent VNS study performed the last VNS surgery in 2008 and the 3 other studies were conducted in the 1990s. The very low-to low-quality evidence suggested that patients undergoing DBS are twice as likely to experience a treatment-related adverse event during the 12 months following surgery than are those who receive VNS.

12. Comparative effectiveness

DBS versus sham DBS or OMT

Effectiveness outcomes in the 2 RCTs were reported for each intervention arm during the double-blind phase as well as for the entire cohort once all patients started receiving active DBS (SANTE trial 2010 and Herrman 2019). In the SANTE trial, the only difference observed between the 2 groups was a 17% reduction in seizures in patients receiving active stimulation. There was no discernible difference between the patient groups with respect to 50% responder rates, seizure severity, quality of life or rates of epilepsy- or device-related hospitalisations.¹⁶ These results do not appear to be affected by prior VNS or epilepsy surgery, although patients with seizures originating from the temporal lobe seemed to have better outcomes than other patients. The

¹⁵ Medtronic Inc. 2022. Deep brain stimulation. *Healthcare professionals*, viewed 22 November 2022, <<https://www.medtronic.com/ca-en/healthcare-professionals/products/neurological/deep-brain-stimulation-systems.html>>.

¹⁶ Medtronic Inc. 2010. Summary of safety and effectiveness data. Implantable multi-programmable quadripolar deep brain stimulation system for epilepsy, viewed 13 October 2022, <https://www.accessdata.fda.gov/cdrh_docs/pdf/P960009S219b.pdf>

smaller RCT of 18 patients was unable to detect any differences in seizure frequency between active and sham DBS after 6 months of follow-up. The authors noted that this may be due, in part, to the small sample size, possible suboptimal electrode positioning in some patients and using fixed stimulation parameters for all patients.

It has been suggested that the effects of DBS accrue over time (months to years) and that shorter follow-up periods may negatively bias against DBS. This is borne out by the extension period of the SANTE trial, which demonstrated a significant reduction in seizure frequency 7 years after treatment: 74% (intention-to-treat [ITT] analysis, 68%) of the remaining 50 patients were 50% responders and had a median reduction in seizure frequency of 75% (ITT analysis, 70%). In contrast, these values for the active treatment arm at 3 months were 30% for responders and a median reduction of 35%. Mean Liverpool Seizure Severity Scale scores had decreased by 37% (N = 67). Although improvements in adjunctive medications and the selective withdrawal of patients who were doing poorly could have confounded these results, the authors of the SANTE trial noted that patients treated with new medications did not improve any faster than those with stable medication regimens. In addition, an analysis of the data using a last-observation-carried-forward imputation found that the results were similar.

An indirect naïve comparison of DBS and OMT (low-quality evidence) indicated that patients in both groups had similar 50% responder rates¹⁷ at 12 months follow-up, but those receiving DBS experienced slightly greater improvements in quality of life. The range of improvement seen in the 2 outcomes shared by the DBS sham and OMT arms of separate RCTs was very similar (50% responder rates were 26% and 24%, respectively; quality of life improvements was 6% and 3%, respectively), suggesting that DBS sham may approximate OMT more closely than was originally thought.

DBS versus VNS

The self-controlled case-series study of 11 patients reported no difference between DBS and VNS in the proportion of 50% responders (46% versus 56%; RR 0.83, 95% CI 0.36, 1.94). However, this study had poor internal validity and a high risk of bias. In addition, even though the patients acted as their own controls, the long period of VNS treatment (ranging from 2.7 to 7.3 years) prior to undergoing DBS means that outcomes for the latter could have been confounded by the fluctuating nature of epilepsy and any other factors influenced by patient age or duration of illness. The length of the washout period between VNS removal or inactivation and DBS implantation was also not reported.

Four of the included RCTs with therapeutic VNS treatment arms provided data on effectiveness outcomes for a naïve indirect comparison with DBS. However, the differing outcomes and follow-up lengths reported in the DBS and VNS studies limited the possible comparisons. In addition, the age of the VNS studies means that they are unlikely to be representative of current practice given that in the most recent VNS study the last VNS surgery was performed in 2008 and the other 3 studies were conducted in the 1990s. The low- to very low-quality evidence suggested that VNS and DBS have similar efficacy in terms of responder rates, reducing seizure frequency and improving quality of life up to 12 months after device implantation.

Clinical claim

The evidence suggests that bilateral anterior thalamus DBS in patients with severe drug refractory focal epilepsy who are ineligible for curative brain surgery has non-inferior effectiveness and inferior safety relative to VNS and non-inferior effectiveness and inferior safety relative to OMT.

¹⁷ The proportion of patients whose seizure frequency is reduced by at least 50% compared with baseline.

This conclusion is based on the combined direct and indirect comparison evidence summarised in Table 11. Indirect evidence from the VNS (k = 4 studies) and DBS treatment arms (k = 2) of separate RCTs suggested that VNS and DBS have similar efficacy in terms of responder rates (k = 3), reducing seizure frequency (k = 3) and improving QoL (k = 2). However, patients undergoing DBS are more likely to experience a treatment-related adverse event than those who receive VNS (k = 2). Limited direct (one very small self-controlled case series study) supported the finding that there is no difference between the two treatments with respect to the proportion of 50% responders. Therefore, it was determined that DBS has equivalent effectiveness and inferior safety compared with VNS. However, the confidence in this conclusion is low since patients in the DBS RCTs likely had more severe epilepsy than those in the VNS studies, and most of the evidence was derived from a naïve indirect comparison.

Direct comparative evidence (k = 2) suggested that DBS and sham treatment have similar safety profiles, but that active DBS is more effective in reducing the frequency of seizures. Indirect comparative evidence from the DBS and OMT treatment arms of two separate RCTs indicated that these treatments are equally effective at reducing seizure frequency, although DBS provides a slightly better improvement in QoL. However, patients receiving DBS are far more likely to experience an adverse event. The range of improvement seen in the 2 outcomes (50% responder rates and QoL improvements) shared by the DBS sham (k = 2) and OMT arms (k = 1) of the separate RCTs were very similar, suggesting that DBS sham may be a closer proxy to OMT than expected. However, the potential confounding influence of the microlesion and placebo effect of DBS surgery makes it difficult to assume that DBS is an equivalent substitute for OMT. Consequently, even though it would appear that DBS is slightly superior to OMT with respect to effectiveness, the confidence in the evidence base is low, necessitating a more conservative judgement of non-inferiority.

Table 11 Summary of the evidence base quality and direction of effect for the DBS comparisons

Comparator	DBS effectiveness		DBS safety	
DBS sham	Superior	⊕⊕⊕⊖ Moderate	Non-inferior	⊕⊕⊕⊖ Moderate
OMT	Non-inferior	⊕⊕⊖⊖ Low	Inferior	⊕⊕⊖⊖ Low
VNS	Non-inferior	⊕⊕⊖⊖ Low	–	–
VNS	Non-inferior	⊕⊕⊖⊖ Low ⊕⊖⊖⊖ Very low	Inferior	⊕⊕⊖⊖ Low

Note: Bolded comparator name indicates direct comparison

Abbreviations: DBS = deep brain stimulation; OMT = optimised medical treatment; VNS = vagus nerve stimulation

13. Economic evaluation

An economic evaluation has been undertaken in this assessment using a cost-utility approach, given the claim of superior clinical effectiveness and non-inferior safety of DBS for treatment of drug refractory epilepsy compared to VNS and OMT. The model estimates costs per year of life, costs per seizure and cost per quality adjusted life year (QALY) gained as an incremental cost-utility ratio (ICUR).

Cost-effectiveness has been conducted for DBS compared with VNS and OMT for adult patients with refractory epilepsy from a health system perspective in a series of steps. The first step (trial step) is for 3 months, reflecting the blinded phase of the pivotal SANTE trial. Extrapolated analyses are undertaken for 7 years (open phase of SANTE trial) and a lifetime analysis.

A Markov model has been developed based on the structure of Chan and colleagues¹⁸ applied in Australia using local resource costs and a range of updated assumptions based on recent studies. There are 4 states in the model: <50% seizure reduction (≥ 10 seizures per month), >50% seizure reduction (0–10 seizures per month), seizure-free and death. Death is an absorbing state to which patients can transition from all states.

Table 12 Summary of the economic evaluation

Perspective	Australian health system
Intervention	DBS
Comparators	VNS and OMT
Type of economic evaluation	Cost-utility analysis
Sources of evidence	SANTE and PULSE trials for base case
Time horizon	3-month trial, 7-year and lifetime extrapolated time horizons
Outcomes	QALYs/ life-years gained/seizures
Computation method	Cohort expected value analysis
Generation of base case	Trial based
Health states	<50% seizure reduction (≥ 10 seizures per month) $\geq 50\%$ seizure reduction (0–10 seizures per month) Seizure-free (0 seizures per month) Death
Transition probabilities	SANTE trial for DBS and Rvlylin PULSE trial for VNS and OMT in base case. Sensitivity analyses were conducted for VNS using E03, E05 and Englot data, along with OMT alone comparison based on the Rvlylin PULSE trial.
Cycle length	3 months
Discount rate	5% used for base, and 3.5% and 7% sensitivity analyses
Software packages used	Microsoft Excel 2010

Abbreviations: DBS = deep brain stimulation; OMT = optimal medical treatment; QALY = quality adjusted life year; VNS = vagus nerve stimulation

The incremental cost and the incremental effectiveness of DBS versus VNS and OMT are presented in Table 13. The ICUR is presented as the incremental cost of achieving an additional QALY. It is evident that the lifetime ICUR is \$143,395 per QALY gained, and the ICUR in trial period is \$1,625,659.

Table 13 Incremental cost utility ratio of DBS vs VNS and OMT

	Discounted cost	QALYs	Seizures	Incremental cost per seizure avoided	Incremental cost (ICUR) per QALY gained
Trial period					
DBS	\$42,818	0.34	108	\$2,601	\$1,625,659
VNS and OMT	\$19,998	0.33	117		
Difference	\$22,821	0.01	-9		
7-years					
DBS	\$68,721	4.67	1,167	\$612	\$381,796
VNS and OMT	\$42,548	4.60	1,210		
Difference	\$26,173	0.07	-43		
Lifetime					
DBS	\$121,997	12.39	4,343	\$122	\$143,395
VNS and OMT	\$78,767	12.09	4,697		
Difference	\$43,230	0.30	-354		

Abbreviations: DBS = deep brain stimulation; ICUR = Incremental Cost Utility Ratio; OMT= optimal medical treatment, QALY= quality adjusted life years; VNS= vagus nerve stimulation

¹⁸ Chan et al., 2022. Economic evaluation of deep brain stimulation compared with vagus nerve stimulation and usual care for patients with refractory epilepsy: A lifetime decision analytic model. *Epilepsia*.

Key drivers of the model are summarised in Table 14. The modelled results were most sensitive to changes in the proportion of long-term responders, costs of the DBS device, cost of hospital stay following implantation and the modelling time horizon.

Table 14 Key drivers of the economic model

Description	Method/Value	Impact
Time horizon	The time horizon of the model was varied from 3 months, 7 years and lifetime (35 years). These periods corresponded with the length of the blinded phase of the SANTE trial, the length of follow-up of the open phase of SANTE and the lifetime analysis in the Chan study.	<u>High, longer projections favour the intervention</u> DBS involves a substantial implantation surgical cost, hospital stay and device cost. These costs are spread over a longer projection of health benefits the greater the extrapolation period. Given that the length of follow-up of the blinded trial was 3 months, there is uncertainty about modelling results beyond this time.
Costs of the DBS device	Costs of the device were calculated using applicant details provided in the PICO. The model assumes the Percept IPG – PC generator will be used, which is valued at \$13,592. There are several other single-use consumables that make the overall DBS device and consumable cost (\$28,983) more expensive than VNS at \$14,504.	<u>High, any reductions favour the intervention</u> DBS implantation was calculated to cost around \$41,861.4, with the device accounting for 70% of the cost. Varying the cost by 20% has a large impact on the estimated ICUR. Reducing the cost of the device would make the intervention more cost-effective
Costs of the hospital care	The MSAC submission for DBS treatment of Parkinson’s disease assumed the AR-DRG BO2B (cranial invention, minor) would be associated with the surgery and have a hospital cost of \$9,768 on top of the procedure. This cost and length of hospital stay is longer than that assumed for epilepsy. The costs of hospital stay was included as a sensitivity analysis.	<u>High, increases in days of hospital stay favour the comparator</u> The base model assumes a hospital stay of 1–2 days, which was indicated by the applicant for DBS surgery associated with epilepsy. Any increases in days of stay for DBS favours the comparator
Varying the proportion of responders	The base model uses the responder proportion at 3 months from the SANTE trial and proportions up to 7 years using the open phase of the trial. The open phase data is not as high quality as that from the shorter term blinded randomised trials.	<u>High, direction uncertain</u> Varying responder proportions has a large impact on model results. The same impact was evident for the VNS arm. The nature of the bias is uncertain but has a large impact on model results.
Utilities	Base model utilities were sourced from the Messori study. The sample of 81 patients used in this analysis was small, so it is difficult to generalise results to the Australian context.	<u>High, direction uncertain</u> Varying utilities by 20% has a large impact on model results. The model does not capture seizure severity, which also limits health benefit calculations

Abbreviations: AR-DRG = Australian Refined Diagnosis Related Groups; DBS = deep brain stimulation; ICUR = incremental cost utility ratio; MSAC = Medical Services Advisory Committee; VNS = vagus nerve stimulation

Key concerns with the economic evaluation are that no head-to-head studies were identified in the clinical evaluation comparing DBS to VNS and OMT, clinical evidence had limited maximum follow-up, and utilities for epilepsy health states were taken from the study of Messori et al., 1998, which had a limited sample of 81 patients. Each of these issues affect parameters that impact economic modelling results.

Sensitivity analyses are presented for the 7-year analysis using the univariate changes outlined in Table 15 and scenario analyses in Table 16. Univariate sensitivity analysis involved changing utility, unit cost, and battery life values by 20% and transition probabilities by 5% to test the robustness of modelling results to key assumptions. Scenario analyses relate to structural assumptions and data sources included in the model. Parameters having the largest impact on results are presented in the following tables.

Table 15 Univariate sensitivity analysis DBS vs VNS and OMT 7-year analysis

Parameter	Analysis	Incremental cost	Incremental effect	ICUR
7-year extrapolation		\$26,173	0.07	\$381,796
Utilities				
≥50% disutility (-0.11)	-0.13	\$26,173	0.06	\$443,786
	-0.09	\$26,173	0.08	\$335,001
<50% disutility (-0.3)	-0.36	\$26,173	0.09	\$285,376
	-0.24	\$26,173	0.05	\$576,616
Costs				
DBS prostheses and single-use consumables (\$28,983)	\$34,780	\$31,970	0.07	\$466,352
	\$23,186	\$20,377	0.07	\$297,239
VNS prostheses and single-use consumables (\$14,504)	\$17,405	\$23,272	0.07	\$339,481
	\$11,603	\$29,074	0.07	\$424,110
DBS battery life (5 years)	6.0	\$25,466	\$0	\$371,484
	4.0	\$26,914	0.07	\$392,607
VNS battery life (7 years)	8.0	\$36,446	0.07	\$531,640
	6.0	\$25,612	0.07	\$373,614
DBS transition probabilities				
<50% seizure reduction → ≥50% seizure reduction	Multiplied by 95%	\$26,220	0.04	\$587,202
	Multiplied by 105%	\$26,127	0.09	\$284,491
VNS transition probabilities				
<50% seizure reduction → ≥50% seizure reduction	Multiplied by 95%	\$26,138	0.09	\$303,025
	Multiplied by 105%	\$26,207	0.05	\$509,518

Abbreviations: DBS = deep brain stimulation; VNS = vagus nerve stimulation; ICUR = incremental cost-utility ratio

Scenarios are included in Table 16 where VNS and OMT arm transitions are based on the results of the E03 and E05 trials and Morris trial, the comparator arm uses the OMT alone arm of Rvylin trial and waning is applied to the DBS and VNS arms. There are no long-term data from trials to support waning assumptions; however, the inclusion of waning has an impact on the ICUR. The inclusion of the waning assumption and use of E03 and E05 trials and Morris data have the largest impact on the calculated ICUR.

Table 16 Scenario sensitivity analyses

Sensitivity analyses	ICUR	Comments
7-year analysis	\$381,796	Results for base model 7-year projection
E03 and E05 trials and Morris data used for VNS arm	\$168,652	The proportions responding at less than 12 months in the E03 and E05 trials are similar to Rvylin. The Morris study reported lower proportions of longer-term responders compared to Englot. The choice of long-term study has a large impact on results.
Comparator assumes Rvylin OMT only results for DBS comparison	\$137,200	The Rvylin trial reported 0.24 response at 12 months but did not specify the seizure-free proportion. These proportions are extrapolated for the remaining period of the model. Costs are sourced from the PBS averaged across a basket of medicines. The comparison has a large impact on results.
Waning applied to DBS and VNS arm (0.01)	\$434,195	Applying waning to both arms has a moderate impact on the estimated ICUR. The nature of waning in clinical practice is unclear.
Waning applied to DBS arm only (0.01)	\$4,521,406	Waning has a large impact on the estimated ICUR. The nature of waning in clinical practice is unclear.
Australian general population utility included for seizure-free state and Messori disutilities applied for non-responder and responder states	\$382,049	Australian general population utility for the seizure-free state and inclusion of disutilities from Messori had limited impact on results
Pathology and imaging costs included as part of disease management costs	\$381,766	Pathology cost inclusion has no impact on results.
Medication costs not included in VNS and OMT arm	\$481,167	Medication cost inclusion had a moderate impact on results
Medication costs not included in DBS arm, only	\$282,413	Medication cost inclusion had a moderate impact on results

Abbreviations: DBS = deep brain stimulation; ICUR = incremental cost-utility ratio; PBS = Pharmaceutical Benefits Schedule; VNS = vagus nerve stimulation

14. Financial/budgetary impacts

An epidemiologic approach is used to estimate the financial impact of the expansion of the DBS item. Firstly, the prevalence of patients with drug refractory epilepsy in Australia is estimated based on an assumed proportion of epilepsy patients taken from the literature and those entering CEPs. Secondly, uptake of the proposed MBS-supported services with restrictions is estimated. The CEP was estimated to include fewer than 500 patients per year, so the costs of expanding the population eligible for DBS is calculated to involve a relatively small number of patients. It is estimated that 30 patients would be implanted with DBS in year 1, either as direct substitution for VNS or as an additional service. Net MBS costs would increase up to \$410,124 per year (See Table 17).

Table 17 Net MBS cost of DBS expanded listing

Year	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Patients with DBS initial implantation	30	36	43	52	62	75
Replacement DBS	0	0	0	0	0	29
Patients with VNS initial implantation	-30	-36	-43	-52	-62	-75
Replacement VNS	0	0	0	0	0	0
MBS Costs						
DBS	\$215,488	\$263,700	\$321,555	\$390,981	\$474,293	\$587,365
VNS	-\$55,932	-\$72,234	-\$91,795	-\$115,269	-\$143,438	-\$177,240
Net cost	\$159,556	\$191,467	\$229,760	\$275,712	\$330,855	\$410,124

Abbreviations: DBS = deep brain stimulation; MBS = Medical Benefits Scheme; VNS = vagus nerve stimulation

Given that the unit cost of the DBS device and the costs of single-use consumables are greater than those for VNS, the largest cost impact is associated with prosthesis supported by private health insurance. These net costs are estimated to increase to \$1,470,514 by year 6. The greatest uncertainty is associated with uptake. PASC noted there is limited potential for leakage as MBS items are already available for other conditions where DBS is used (e.g. Parkinson's disease). The size of CEPs and limited number of medical professionals able to perform the service also limit uptake.

15. Other relevant information

Nil

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- The quality and volume of the evidence were low. Many of the trials presented were older (>7 years old) and had several limitations. No head-to-head studies were identified which compared DBS to VNS and OMT.
- The claim of non-inferior safety was not supported by the evidence, and is more likely to be inferior for both comparators largely due to the invasive nature of DBS.
- The clinical claim of superior effectiveness was not supported by the available evidence. There appears to be a lack of high-quality long-term data, and the suggestion that DBS response improves over time does not appear to be clearly supported with confidence by the data presented.
- The descriptors should restrict the age of patients to adults >18 years old, specify the location to be targeted by DBS (anterior thalamus) and specify that DBS should be restricted to patients with focal epilepsy only.
- Comprehensive Epilepsy Programs (CEPs) were not well defined and are not delivered in all jurisdictions or regional centres. They appear to comprise a multidisciplinary team component but further advice may be needed to clarify the service delivery.
- Only Medtronic equipment is indicated for epilepsy and listing this for epilepsy as requested would result in Abbott and Boston Scientific equipment being used off-label. This issue should be resolved before listing.

Economic issues:

- The results of the economic evaluation were uncertain. The cost-utility analysis was inappropriate because the clinical evidence did not support the clinical claim of superiority. The clinical evidence suggested non-inferior effectiveness and inferior safety relative to VNS and non-inferior effectiveness and inferior safety relative to OMT.
- The 7-year and lifetime economic modelling extrapolations are not supported by clinical evidence, making the ICERs uncertain.
- The utilities may not be directly applicable to the Australian population.
- DBS has a higher cost than VNS and OMT. The device cost, surgical costs and in-hospital length of stay are large cost components.

Financial issues:

- The financial analysis assumes that the low patient numbers and uptake will be maintained due to the limited access to CEPs (which treats up to 500 patients only in Australia each year). However, there was uncertainty in whether the uptake could increase if CEPs are expanded to deliver care to more patients.

ESC discussion

ESC noted that this application was from the Neurosurgical Society of Australasia to amend an existing suite of Medicare Benefits Schedule (MBS) items for bilateral deep-brain stimulation (DBS), to include drug refractory epilepsy as an additional (new) indication. ESC noted the comparators were vagus nerve stimulation (VNS) and optimised medical treatment (OMT). ESC considered the comparators VNS and OMT to be appropriate.

ESC noted the consultation feedback stating that DBS increased the treatment options available and the potential subsequent improvement in epilepsy control could result in patients' increased independence, improved relationships with others, and reduced reliance on support services/family. ESC also noted the disadvantage of having to replace the stimulator box for non-rechargeable devices and queried whether wireless charging was available for devices such as that proposed.

ESC noted that, currently, only Medtronic equipment is ARTG listed for the epilepsy indication. This may result in DBS devices manufactured by Abbott and Boston Scientific being used off-label – ESC considered that this risk of off-label use needs to be resolved.

ESC noted that the application proposes to amend the MBS item descriptors for 40851, 40852, 40854, 40856, 40858, 40860 and 40862 for DBS treatment of Parkinson's disease, essential tremor or dystonia to add "Drug refractory epilepsy in patients not suitable for resective surgery following assessment by a Comprehensive Epilepsy Program (CEP)" as an additional indication. ESC advised, based on the evidence, that the descriptor should specify the age of the patients concerned (adults 18 years of age and older), the location in the brain to be targeted by DBS (anterior thalamus) and restrict it to patients with focal epilepsy only. ESC also noted that resective surgery may be refused by the patient, contraindicated or may be unsuccessful in halting seizures if the patient does receive it so this should be reflected in the item descriptors as well.

ESC considered that CEPs required further definition to understand their structure, process, performance and outcomes. ESC noted it would be difficult to guarantee similar service delivery when it can vary across state and territory jurisdictions and over time. ESC noted there is a lack of regional access to CEPs. For example, there are no CEPs in Tasmania, the Australian Capital Territory or the Northern Territory. ESC considered that CEPs likely comprise a multidisciplinary team and are likely to be based in metropolitan specialist treatment centres, but ESC could not identify a reliable definition of CEP, even using overseas information, to support this assumption. ESC considered that since CEP may be a variable service, that details should be considered to be included in the descriptor or explanatory notes to ensure the expectation of CEP being delivered as multidisciplinary care.

ESC noted that the current MBS item descriptors encompass both unilateral and bilateral DBS treatment for Parkinson's patients and considered that this needs to be maintained if the proposed service were to be supported by MSAC. ESC noted that the Department stated that MBS item 40862 would likely be provided during the initial procedure where the Multiple Operation Rule would apply, but subsequent postoperative programming would be performed by a neurologist in an outpatient setting. ESC agreed with the Department proposal to retain the T8 programming item for the initial procedure and introducing a DBS programming item for ongoing management, an item for the unilateral programming and an item for bilateral programming under Cat 2 –

Diagnostic Procedures and Investigations. ESC considered that, since DBS is used to treat other indications already, further clinician training would not be necessary, assuming the same trained clinicians would provide the proposed service.

ESC noted the proposed clinical management algorithm adds the intervention as an alternative treatment option to VNS or when VNS had failed to provide adequate epilepsy control. ESC noted OMT may involve drug substitution or drug withdrawal.

ESC noted that the available evidence was limited. ESC noted there are no direct trials comparing OMT to DBS, but two randomised controlled trials (RCTs) comparing DBS to sham DBS surgery were presented. For these RCTs, ESC considered the risk of bias to be low, but was concerned about the validity of the sham procedure. Four RCTs were used as benchmark data/naïve comparison (with a low-moderate risk of bias). ESC noted another self-controlled case series trial comparing DBS to VNS but considered there to be a high risk of bias in this study. ESC noted the following limitations to all the trials:

- small population sizes
- limited to patients with focal epilepsy
- limited duration for outcome data collection (there is a suggestion that the effect of DBS accumulates over time, so these studies may risk underestimating the effect)
- age of study participants is 28–40 years, so the studies miss patients outside of these age groups
- studies were conducted 7–30 years ago, so advancements/improvements in the technology may not have been captured.

ESC noted the pre-ESC response presented recent evidence from the Australian ESTEL trial¹⁹ for people who had generalised epilepsy. The results for DBS appeared to be favourable and appeared to support ongoing improvement over time. However, ESC considered this evidence to be out of scope for this application, because the trial population only encompassed patients with a specific neurological condition (Lennox-Gastaut syndrome) and the DBS targeted the centro-median thalamus, not the anterior thalamus. ESC noted two ongoing or recently completed clinical trials on DBS; one was recruiting and aims to examine long-term safety and effectiveness of DBS²⁰ and the other trial aimed to examine the effectiveness of DBS in focal or multifocal epilepsy and was completed in November 2021²¹ but no results are currently available.

ESC considered the evidence from the two trials supporting the safety outcomes to be of moderate quality. ESC noted the SANTE trial (2010) reported a rate of serious device-related adverse events (AEs) of 35%; of these, lead malposition (8%) and implant site infection (4%) were the most frequently reported AEs. Over the 7-year follow-up period, there was no difference in cognitive decline/depression or neuro-behavioural issues compared to baseline. ESC also noted fewer epilepsy-related injuries in the stimulation group (risk ratio = 0.29 at three months). ESC considered that the indirect naïve comparison between DBS and OMT (low-quality evidence) suggests that patients undergoing DBS are four times more likely to experience an AE and 30 times more likely to experience a serious AE. ESC also noted treatment-related AEs are two times more likely for DBS than for VNS. ESC considered that DBS is more invasive than its comparators and involves a surgical approach into cerebral tissue, so the complications, although rare, are likely to have significantly greater clinical consequence than the adverse events related to VNS and OMT. ESC considered epilepsy related injuries may more appropriately be considered as an effectiveness outcome (with an inverse relationship to effectiveness) rather than a safety outcome, but inclusion

¹⁹ Dalic *et al.*, DBS of Thalamic Centromedian Nucleus for Lennox-Gastaut Syndrome (ESTEL Trial). *Ann Neurol.* 2022

²⁰ <https://clinicaltrials.gov/ct2/show/NCT03900468>

²¹ <https://clinicaltrials.gov/ct2/show/NCT02076698>

as a safety outcome could explain the rationale for the applicant's claim of non-inferior safety for the intervention.

Regarding comparative effectiveness, ESC considered the effectiveness outcomes of relevance are captured: seizure frequency and severity, quality of life (QoL) and healthcare utilisation. ESC noted that the SANTE trial showed that DBS was associated with a 17% reduction in frequency of seizures compared to sham DBS/OMT, but no change in seizure severity, QoL or hospitalisation rates. The 7-year follow-up of the SANTE trial showed that 74% of patients remaining in the study had a median seizure frequency reduction of 50%. ESC considered that these results may potentially be confounded by the withdrawal of non-responders from the study during follow-up. When comparing DBS to VNS, ESC noted there was no difference in the proportion of patients in whom seizure frequency had reduced by 50%, but this study was at a high risk of bias. ESC noted the patients in the DBS RCTs appeared to have more severe epilepsy than those in the VNS studies, so ESC considered these results to be uncertain. Other sources of uncertainty relate to the age of the data and the potential for improvements in device technology to affect outcomes. ESC considered there to be a lack of high-quality long-term data, and the suggestion that DBS response improves over time does not appear to be clearly supported with confidence by the data presented.

ESC noted that the aim of DBS is to reduce the frequency and severity of seizures, and to improve QoL. ESC noted the application made the clinical claim that DBS is superior in effectiveness and non-inferior in safety to both comparators. ESC considered that the evidence does not support the claim of non-inferior safety for DBS versus both comparators and considers it inferior. ESC considered the claim DBS is superior in effectiveness compared with VNS and OMT was not supported by the evidence.

ESC noted that the economic evaluation was a cost-utility analysis, with extrapolated time horizons of 7 years and lifetime (from a 3-month base case as used in SANTE [DBS] and Rvylin PULSE [VNS and OMT] trials). Outcomes measured were quality-adjusted life years (QALYs), life-years gained and seizures. The model was simple with four health states: seizure free, >50% reduction in seizures, <50% reduction in seizures, and death. ESC considered the model to be inappropriate because a cost-utility analysis is based on the assumption of clinical superiority, which ESC considered was not supported by the evidence. ESC considered the clinical evidence suggested non-inferior effectiveness and inferior safety relative to VNS and non-inferior effectiveness and inferior safety relative to OMT. In addition, the utility estimates were from a small ($n = 81$), older (1998) Italian study conducted as part of an evaluation of adjunctive lamotrigine therapy, which may limit its applicability for the Australian population. ESC noted that the key driver of the incremental cost-effective ratios (ICERs) was the time horizon, with longer extrapolations favouring the intervention, giving ICERs of \$1,625,659/QALY (3 months), \$381,796/QALY (7 years) and \$143,395/QALY (lifetime). ESC considered these ICERs to be uncertain because the extrapolation is based on lower quality 'open phase' data. ESC noted that the cost of the device and hospital care, and the percentage of responders were also important drivers of the ICER. ESC also noted that non-responders were included in the <50% reduction in seizures health state and considered that this affected the results but was uncertain if data were available to separate non-responders into their own health state. ESC was also concerned about the translation of clinical evidence into the economic evaluation because the clinical evidence was of low quality.

ESC noted that an epidemiological approach was used to estimate the financial impact. ESC noted that the financial analysis assumes the uptake will be 30 people in Year 1, increasing to 75 by Year 6. ESC noted this would result in a modest net cost to the MBS of \$159,556 to \$410,124 over six years, assuming DBS would substitute for VNS at 100%. However, ESC noted some patients may receive DBS after VNS as well. ESC was uncertain with the accuracy of the small, estimated population due to the prevalence of epilepsy in Australia being approximately 0.6%,

equating to 151,000 people²². ESC considered that if the drug refractory epilepsy population was approximately 30-40% of those patients (see section 5) then the number of eligible patients may be approximately 45,000-60,000 people. However, ESC noted that the CEPs, which eligible patients must be assessed by, are estimated to care for only 500 patients per year across Australia (see section 12) so their capacity would limit the uptake. ESC queried whether the uptake for DBS could significantly increase or potential leakage could occur if the CEPs are expanded in future. ESC noted that the highest increases in cost would be in relation to the prostheses costs to private health insurers. ESC noted that a number of devices are currently listed on the Prostheses List, with the Medtronic sponsored device the only device indicated for use in epilepsy in Australia.

17. Applicant comments on MSAC's Public Summary Document

The Applicant would like to acknowledge their disappointment at the outcome of the MSAC review. It was stated that the evidence presented was relatively old, but this is because DBS for epilepsy is routinely available in most major centres across Europe and North America and is no longer the subject of active research. While we accept the concerns raised during the review, we are disappointed with the interpretation of the positive outcomes of the landmark, randomised control trial (SANTE) and the 10-year follow-up study. SANTE did not contain a prolonged head-to-head comparison between DBS and optimal medical therapy (OMT), because it is not possible to perform that study blinded over prolonged periods. Inserting a device and leaving it 'off' for prolonged periods is ethically unacceptable, and hence the pivotal studies (e.g., SANTE) had a relatively short, 3-month blinded phase. Despite this, the pivotal studies showed a treatment benefit of DBS over OMT, and follow-up open label studies have shown progressive benefit over time, consistent with the therapeutic effect of DBS being due to neuromodulation of epileptic circuits, rather than 'seizure blocking'. The 10-year SANTE follow-up study in 2021 concluded that the long-term efficacy and safety profiles of DBS for epilepsy were favourable and stable, and the reduced frequency of the most severe seizure types would likely improve SUDEP rates (sudden unexpected death in epilepsy) (Salanova et al 2021). We are concerned that the lack of public funding for DBS further widens the gap between the standard of care provided to Australians with the most difficult to treat epilepsies, compared to other first world nations, given the lasting benefits reported for DBS treatment (e.g., reduced seizure frequency, meaningful improvements in QOL).

Salanova V et al. SANTÉ Study Group. The SANTÉ study at 10 years of follow-up: Effectiveness, safety, and sudden unexpected death in epilepsy. Epilepsia. 2021 Jun;62(6):1306-1317. doi: 10.1111/epi.16895. Epub 2021 Apr 8. PMID: 33830503.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)

²² <https://www.aihw.gov.au/reports/chronic-disease/epilepsy-in-australia/contents/how-many-australians-have-epilepsy>