Australian Government

Department of Health

MSAC Application 1701

Deep brain stimulation of the thalamus for the treatment of severe refractory epilepsy

Ratified
PICO Confirmation

Summary of PICO/PPICO criteria to define question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Table 1 PICO for deep brain stimulation of the thalamus for the treatment of severe drug-resistant epilepsy: PICO Set 1

Component	Description
Population	Adults with severe drug-resistant epilepsy, i.e., epilepsy which has not been adequately controlled with medication, and where resection of the brain is either contraindicated or has been unsuccessful in halting seizures.
Intervention	Deep brain stimulation (DBS) of the thalamus
Comparator	• Vagus nerve stimulation (VNS) • Optimised medical treatment/ best supportive care
Outcomes	• Safety o Serious adverse events (neurologic & physical) o Procedure-related adverse events, e.g., haemorrhage, implantation site infection o Adverse events/complications, e.g., depression, memory impairment • Clinical effectiveness Primary outcomes: o Reductions in seizure frequency and severity (seizure-free days/months, proportion of patients with a 50% seizure reduction) o Quality of life/Activities of daily living, measured using an appropriate tool (e.g., Washington Psychosocial Seizure Inventory, the Social Effects Scale, the Epilepsy Surgery Inventory, Quality of Life in Epilepsy Inventory (QOLIE), Liverpool QOL Battery, Liverpool Seizure Severity Scale (LSSS), Epilepsy Risk Awareness Scale (ERA), Generalised Anxiety Disorder Scale-7 (GAD-7), Global Assessment of Severity of Epilepsy (GASE) 7-point scale) Secondary Outcomes: o Decrease in sudden death from epilepsy (SUDEP) o Decrease in seizure-related injuries o Decrease in hospital admissions for seizure-related injuries o Decrease in carer stress. • Cost-effectiveness o Cost per life-year gained o Cost per quality-adjusted life-year (QALY) gained • Healthcare resources o Cost of intervention delivery o Cost associated with changes in clinical management (e.g., follow-up) • Total Australian Government healthcare costs: o Total cost to the Medicare Benefits Schedule (MBS) o Total cost to other healthcare services.
Assessment questions	What is the safety, effectiveness and cost-effectiveness of DBS of the thalamus *versus* VNS for treatment of severe drug-resistant epilepsy?

Purpose of application

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

The PICO has referred to severe refractory epilepsy as severe drug-resistant epilepsy, consistent with the terminology used by the International League Against Epilepsy.

The applicant expects that compared to vagus nerve stimulation (VNS), DBS of the thalamus for the treatment of drug-resistant epilepsy [when the patient is not suitable for curative brain surgery] will have:

- Superior clinical effectiveness
- Non-inferior safety.

The overall aim of DBS therapy is to reduce the frequency and severity of epileptic seizures and improve the quality of life in patients with drug-resistant epilepsy, who have considered and/or trialled other pharmacological and surgical approaches without success.

PICO criteria

Population

The intervention is intended for patients with epilepsy who continue to experience seizures despite the use of two or more antiepileptic medications at therapeutic doses (i.e., drug-resistant). Eligible patients will have been considered for alternative treatment options such as curative-intent resective brain surgery, and these therapies would have been either a) deemed not appropriate, or b) previously trialled without success. While curative-intent resective brain surgery is currently considered a gold standard in patients with severe drug-resistant epilepsy and may bring seizure relief in up to 70% of patients (the expected outcome of surgery is seizure control with medication (Mayo Clinic, 2021)), it may not always be suitable if large areas of the brain, brain networks, or several foci (e.g., tuberous sclerosis) are involved, or when adverse effects of the surgery may cause other functional deficits not acceptable to the patient.

Lastly, all eligible patients will have been referred to and assessed by a Comprehensive Epilepsy Program. The Comprehensive Epilepsy Program is a 1-2-week inpatient program providing comprehensive assessment of patients with uncontrolled epilepsy. People with both generalised and focal seizures may be eligible for assessment within the program. The program aims firstly to determine the nature and type of the patient's episodes. Secondly, the program aims to determine whether surgical treatment of epilepsy may be suitable. Tests conducted during the program include video electroencephalography (VEEG) monitoring, assessment by a neuropsychologist, assessment for mood disorders, neurosurgical assessment of safety and feasibility of surgery, and neuroradiological investigations. Centres offering Comprehensive Epilepsy Program are generally affiliated with tertiary care hospitals. There are currently 11 centres offering Comprehensive Epilepsy Program in Australia, located in Melbourne, Sydney, Brisbane, Perth, and Adelaide. There are no centres offering the Program in Tasmania, Northern Territory or in the Australian Capital Territory.

PASC confirmed that the application proposes an amendment to the eligible patient population for deep brain stimulation (DBS) to encompass people with drug-resistant epilepsy where resection of the brain is either contraindicated or has been unsuccessful in halting seizures. PASC advised this included both focal

and generalised epilepsy. PASC noted that currently there is limited evidence for the use of DBS in generalised epilepsy and advised that this population should be considered when sufficient evidence is available.

Defining epilepsy

Epilepsy is a serious neurological condition affecting people of all ages, characterised by a tendency for recurrent, convulsive, or non-convulsive unprovoked seizures. Certain triggers may increase the risk of seizures and recognition of known triggers may help reduce/avoid seizures (e.g., fatigue, stress, illness). The term 'epilepsy' is an umbrella term for a diverse range of neurological disorders that includes many different seizure types and syndromes, with diverse aetiologies, and variable prognoses. An epilepsy syndrome is defined by features including family history, age of seizure onset, seizure type(s), cause, and other linked diseases/conditions, progression of the syndrome over time, the presence or absence of brain abnormalities, imaging findings, as well as response to medication (Epilepsy Action Australia). Diagnosis of epilepsy by syndrome is useful for determining treatment options, prognosis, and genetic ramifications.

The International League Against Epilepsy (ILAE) defines epilepsy in the presence of any of the following conditions (Fisher et al., 2014):

1. At least two unprovoked seizures occurring more than 24 hours apart
2. One unprovoked seizure and a probability of further seizures, similar to the general recurrence risk (≥60%) after two unprovoked seizures, occurring over the next 10 years and/or
3. Diagnosis of an epilepsy syndrome.

Some people meet the criteria for epilepsy at the time of a first seizure.

Seizures are generally classified as being focal or generalised, reflecting whether seizures begin in one or more part(s) of the brain (i.e., focal), or both sides of the brain simultaneously (i.e., generalised). The signs and symptoms of a seizure are determined by the brain regions involved. Generalised seizures involve the whole brain and symptoms can affect the whole body, with effects ranging from brief periods of impaired responsiveness and awareness to full body convulsions and loss of consciousness, lasting minutes to hours. Focal seizure effects are determined by the region of brain where the seizure is present (e.g., a seizure in the region that controls the arm will result in uncontrollable jerking of the respective limb). They generally last a few minutes, and the person may remain in a state of confusion for minutes or hours afterwards.

Epilepsy can begin at any age but is somewhat more commonly diagnosed in childhood or older age. The aetiology of epilepsy is multifactorial and the ILAE broadly classifies epilepsy in six aetiological categories, including genetic, structural, metabolic, immune, infectious, or unknown (around 50%) causes (Scheffer et al., 2017). Age at first seizure may also influence epilepsy causation. In adults, epilepsy is often due to acquired vascular, degenerative, or neoplastic aetiologies, while epilepsy with onset in childhood is more often due to genetic, metabolic, or congenital structural abnormalities (Schachter, 2021).

Management/treatment

The management of epilepsy is aimed at controlling seizures, avoiding treatment side effects, and maintaining or restoring quality of life. First-line treatment involves the use of antiepileptic medications selected based on seizure type, potential adverse events, drug interactions with other medications, comorbid conditions, age, gender, childbearing plans, lifestyle, and patient preferences. If antiepileptic medications do not control seizures, then brain surgery and neuromodulation may be considered. Surgery involves removal of the epileptic focus via resection or ablation. Neuromodulation options are non-

destructive alternatives, which involve stimulation of specific neuroanatomical brain structures with the aim of modulating hyperexcitability in their circuits (e.g., VNS, responsive neural stimulation [RNS], and DBS).

If the first medication prescribed fails to stop seizures, addition of a second antiepileptic medication is usually recommended, either in monotherapy or in combination (Kwan et al., 2010). The probability of successful seizure control reduces with each failed medication trial. A 30-year longitudinal study reported that around 50% of patients with newly diagnosed epilepsy achieved seizure freedom with the first antiepileptic medication trialled, and a further 12% of patients become seizure free after trialling a second medication. Only 6.5% of people subsequently stop having seizures after failing a second or third medication trial, leaving 30-40% of people with drug-resistant epilepsy, also called medically refractory epilepsy (Chen et al., 2018). The suggested prevalence of drug-resistant epilepsy is corroborated by the findings of 2021 systematic review and meta-analysis of 103 observational studies, which reported a 36.3% prevalence of drug-resistant epilepsy in clinic-based cohorts and higher rates in people with focal epilepsy (Sultana et al., 2021). Drug-resistant epilepsy has been described as a multifaceted problem (French, 2007) and people with drug-resistant epilepsy are candidates for second-line treatment options.

Prognosis

Approximately two thirds of people with newly diagnosed epilepsy generally have a good prognosis for full seizure control and eventual discontinuation of antiepileptic medications. The most important positive predictor of long-term prognosis is early response to treatment. Different prognostic patterns can be identified, suggesting that the epileptogenic process is not static (Beghi et al., 2015). Four different prognostic groups have been described for people with epilepsy syndrome (Beghi et al., 2015):

- around 20-30% of people have a high probability of spontaneous remission (i.e., excellent prognosis);
- a good prognosis occurs in 30-40% of people who easily achieve pharmacological control and possible spontaneous remission;
- approximately 10-20% have a drug-dependent prognosis, where seizures respond to antiepileptic medications but tend to relapse after treatment withdrawal, and
- 20% have a poor prognosis, where seizures recur despite intensive treatment.

A person's response to antiepileptic medications may be influenced by the type of epilepsy they have, the underlying syndrome and aetiology, as well as the patient's history of seizure frequency, severity, and clustering. Environmental factors, such as trauma and prior drug exposure, as well as genetic factors (including absorption rates, metabolism, and uptake of a medications by target tissue) may potentially impact on an individual's response to pharmacotherapy (French, 2007). The estimated average duration of active epilepsy is around 10 years, based on calculations derived from prevalence and incidence data (Beghi et al., 2015). Population studies following newly diagnosed epilepsy cases for several decades report that up to 80% of people may enter prolonged periods of seizure remission and up to 50% continue to be seizure-free after treatment discontinuation (Sillanpää & Schmidt, 2006).

Burden of disease

Epilepsy is a chronic disease which may profoundly impact a person's quality of life and can be debilitating, conferring serious adverse effects on personal lives and capacity to maintain employment.

Epilepsy has been linked with increased rates of comorbidities which adversely affect quality of life and life expectancy. People with epilepsy have a greater likelihood of experiencing psychiatric conditions, fractures, motor vehicle accidents, cardiovascular disease, sleep disorders, neurodevelopmental disorders, and migraines, on top of the stigma that a diagnosis of epilepsy carries. For example, depression and anxiety are commonly reported in people with epilepsy. Significantly increased odds of active and lifetime depression have been reported in people diagnosed with epilepsy (lifetime prevalence of depression 13.0%, 95% confidence interval (CI) 5.1-33.1%; Fiest et al. (2013)). The unpredictable nature of seizures poses additional dangers for personal safety. Epilepsy is also associated with an increased risk of premature death, relative to the general population (Beghi et al., 2015).

People with epilepsy are at increased risk of sudden unexpected death in epilepsy (SUDEP), which is defined as "the sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in patients with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which post-mortem examination does not reveal a toxicologic or anatomic cause of death" (Nashef et al., 2012). The causes of SUDEP are multifactorial and may include respiratory or cardiac dysfunction. Review of data from people (n=57,775) with a hospital-based ambulatory care or hospital discharge diagnosis of epilepsy in the Swedish National Patient Registry over 1998–2005 (Sveinsson et al., 2017) reported that death certificates underestimate the incidence of SUDEP. Death certificates mentioned epilepsy in 63% of SUDEP cases and the risk of SUDEP was especially underestimated in boys and older people (regardless of sex). People with epilepsy and psychiatric comorbidities also had an increased risk for SUDEP. A recent systematic review suggested that the genetic causes of SUDEP are not well understood because of the limited availability of crucial clinical data such as ECGs and formal cardiac and neurologic pathology evaluations to further elucidate causation in SUDEP cases (Chahal et al., 2020). People living with epilepsy have a risk of up to 1.2 in 1,000 of SUDEP per year, translating into around 171 SUDEP-related deaths annually in Australia (Epilepsy Foundation).

People with drug-resistant epilepsy have a greater burden of disease compared to people with epilepsy who become seizure-free. Drug-resistant epilepsy is associated with serious psychosocial consequences, cognitive problems, and reduced quality of life. Specifically, ongoing seizures are associated with increased rates of anxiety and depression, higher rates of unemployment and underemployment, and loss of independence, including from inability to drive. Poorer outcomes occur across the life span for people with drug-resistant epilepsy. For example, in infants and young children, drug-resistant epilepsy is associated with developmental delay, while in older children and adults it is associated with severe disability and morbidity (Engel, 2016).

Around 250,000 Australians (~ 1% of the population) are currently diagnosed with epilepsy (Epilepsy Action Australia). An Australian Bureau of Statistics 2017-2018 National Health Survey reported that 0.6% of Australians of all ages were living with epilepsy (active cases). It is projected that about 800,000 Australians will develop epilepsy in their lifetime; approximately 3% of the population (Epilepsy Action Australia).

Epilepsy is the second most burdensome neurological condition after dementia in Australia (Australian Institute of Health and Welfare (AIHW), 2016). The total annual cost of epilepsy in Australia in 2019-2020 was estimated to be $12.3 billion, where $4.2 billion of this amount reflected the financial costs of epilepsy. The biggest financial cost $2.3 billion was productivity loss (the impact of epilepsy on a person's lifetime productivity). Other financial costs were costs to the healthcare system ($557.1 million), the cost of informal care ($438.2 million), equipment ($8.6 million), transportation costs ($9.9 million) and deadweight losses ($821.6 million), that is losses from government payments and taxation forgone (Deloitte, 2020). The balance of the annual cost of epilepsy reflects the burden of the disease and loss of

wellbeing and was estimated to be $8.2 billion (based on the value of a statistical life-year and the disability-adjusted life-years lost due to epilepsy) in 2019-2020. The annual burden of disease conferred by epilepsy in Australia was greater than prostate cancer and similar to Parkinson's disease and lung cancer (Deloitte, 2020). The total lifetime cost of epilepsy was estimated to be $22.2 billion for the 14,603 new cases of epilepsy diagnosed in Australia in the period 2019-2020.

Modelling suggests that modest improvements in seizure control can lessen the economic burden of epilepsy. Using life-table modelling and data from 2017, a study by Foster et al. (2020) followed Australians of working age with epilepsy until 70 years of age and predicted over 14,000 excess deaths, more than 78,000 years of life lost, and over 146,000 productivity-adjusted life-years lost due to epilepsy, amounting to a gross domestic product (GDP) loss of A$32.4 billion. The model showed that improving seizure freedom by 5%, for a 75% seizure freedom rate, reduced health care costs and saved years of life, translating to A$3.9 billion savings. A$7.8 billion GDP savings were reported for a 10% improvement in seizure freedom and a seizure freedom rate of 80%.

Target group

Eligibility for DBS of the thalamus for epilepsy will be limited to patients who continue to experience seizures despite the use of two or more antiepileptic medications at therapeutic doses (i.e., drug-resistant epilepsy). Eligible patients will have been considered for alternative treatment options such as curative resective brain surgery, and these therapies would have been either a) deemed not appropriate, or b) previously trialled without success. Lastly all eligible patients will have been referred to and assessed by a Comprehensive Epilepsy Program.

According to the ILAE, drug-resistant epilepsy occurs when a person has failed to become (and stay) seizure-free with adequate trials of two antiepileptic medications, chosen appropriately for the person's seizure type, tolerated by the person, and tried alone or together with other antiepileptic medications (Kwan et al., 2010). The frequency and severity of seizures is generally not considered in the definition, although these vary among people with drug-resistant epilepsy and may help inform future treatment decisions (Berg & Kelly, 2006; Dlugos, 2001).

The probability of achieving seizure freedom in newly diagnosed patients with epilepsy has not changed considerably, despite the availability of new antiepileptic medications in recent decades (Engel, 2016; Perucca et al., 2020). Around 30-40% of patients are diagnosed with drug-resistant epilepsy after trials of antiepileptic medications and need to explore other treatment options (Chen et al., 2018).

PASC confirmed that the patient population includes those with severe drug-resistant epilepsy where two or more medications have been previously used. A specialist neurosurgeon confirmed that the threshold for this procedure in the UK in 2020 was defined as failure of two antiepileptic medications, which is consistent across most of the world. PASC acknowledged that these patients are considered for escalated treatment options such as curative-intent brain resective surgery, and are likely to have tried and failed more than the minimum number of antiepileptic medications, but are either not suitable for the surgical treatment, or the surgical treatment did not provide expected relief.

People with drug-resistant epilepsy experience the greatest burden of epilepsy-related disabilities and higher mortality and morbidity. This includes greater adverse medication effects, higher levels of stigma and social handicap (e.g., poor academic performance, unemployment), higher somatic and emotional comorbidities, and poorer quality of life (Beghi et al., 2015) and an increased morality rate, around 5-10% higher than that of the general population (Engel, 2016). The economic impacts of drug-resistant epilepsy are also significant. For example, in the United States around 40% of people continue to experience

seizures despite appropriate treatment with antiepileptic medications (Kobau et al., 2008) and this subgroup accounted for 80% of the total cost of epilepsy in 2000 (Begley et al., 2000).

PASC noted that the application refers only to adult patients. The applicant noted that while studies are underway in paediatric population, the evidence base for DBS in the paediatric population is currently insufficient.

Investigation, management & referral

Upon diagnosis of drug-resistant epilepsy by their treating neurologist, patients should be referred to a Comprehensive Epilepsy Program for further evaluation. Initial assessment of suspected drug-resistant epilepsy includes review of the electrical and clinical features of the seizures, family history, and review of current and prior antiepileptic medications trialled. Careful review of neuroimaging is particularly important, as this may reveal subtle abnormalities that could provide a target for curative resective epilepsy surgery.

Patients requiring further evaluation are usually referred for a period of inpatient VEEG monitoring with neuropsychology assessments, as well as additional structural and functional brain imaging, including high quality magnetic resonance imaging (MRI), and positron emission tomography (PET) (Schuele & Lüders, 2008). Studies show that early referral to a Comprehensive Epilepsy Program provides patients with the best prospect of seizure freedom avoiding adverse outcomes associated with treatment resistant epilepsy, including irreversible psychological and social problems, disability, and death (Engel, 2016).

When evaluating drug-resistant epilepsy, patients may be encouraged to keep a seizure diary for a nominated period, to help document response to therapy changes and provide insight into potential seizure triggers (Sirven, 2021). Data captured in the seizure diary may include information about any seizures experienced and other related information that may impact on seizure episodes (e.g., use of antiepileptic medications and other medications, details about sleeping patterns such as the amount and quality of sleep).

Utilisation estimates

The Australian Bureau of Statistics recently estimated the population prevalence of active epilepsy was 0.6% (6 per 1,000 people) using data from a National Health Survey 2017-18. Based on this prevalence data, a Deloitte Access Report estimated that around 150,00 Australians are living with active epilepsy (Deloitte, 2020). After undertaking their own modelling to provide a more accurate figure, Deloitte reported that a total of 142,740 people were living with active epilepsy in 2019-20. Prevalence estimates reported for the Australian population are validated by international literature (Deloitte, 2020).

Assuming around 150,000 Australians have active epilepsy (Deloitte, 2020) and given that 30-40% of people are reported to have drug-resistant epilepsy (Chen et al., 2018), it would be expected that 45,000 to 60,000 Australians of all ages have drug-resistant epilepsy.

Only a fraction of people with drug-resistant epilepsy in Australia are referred to a Comprehensive Epilepsy Program, a fact supported by international literature, which reports that fewer than 1% of patients with drug-resistant epilepsy are referred to a Comprehensive Epilepsy Program (Engel, 2016).

PASC discussed concerns about leakage into the patient population eligible for resective surgery but desiring a less invasive procedure. It was concluded that there was little risk for leakage because for patients with focal epilepsy suitable for surgery, resective surgery is strongly preferred (where feasible) due

to its curative intent. DBS would be an inferior option because it can offer meaningful seizure reduction, but not a cure. DBS may be offered to patients with epilepsy amenable to surgical treatment in situations where the surgical risk of open craniotomy is too high, or where patients refuse surgical treatment based on strong personal, cultural, or religious beliefs.

Intervention

The proposed health technology, bilateral DBS of the thalamus, is a therapeutic medical service. DBS therapy is indicated in people with epilepsy that have not been adequately controlled with antiepileptic medication (drug-resistant epilepsy) and where resective brain surgery is either not an option or has been unsuccessful in halting seizures. It is used in both focal and generalised seizures, and, according to the applicant, appears to have similar effectiveness for both. DBS delivers electrical impulses to a key central location deep in the brain, suppressing the bursts of epileptic discharges that characterise seizures. Under general anaesthetic, a neurosurgeon places electrode leads into the thalamus of the brain 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 neurostimulator device (like a pacemaker) implanted in the upper chest. After implantation, the frequency and amplitude of the delivered electrical stimuli are adjusted to maximally suppress the frequency and severity of seizures.

DBS involves a new approach to managing sub-groups of the population with epilepsy in Australia, specifically people with drug-resistant epilepsy. The therapy involves the use of a DBS device. Note, DBS for epilepsy was approved in 2018 by the US Food and Drug Administration as adjunctive therapy for adult patients with partial onset seizures who are drug-resistant to three or more antiepileptic medications (Voelker, 2018).

The delivery of DBS for epilepsy will only be undertaken by neurosurgeons in conjunction with neurologists. It is intended to be provided in inpatient setting (public or private hospitals).

The proposed medical intervention is intended for adults. While studies are currently underway for paediatric DBS application in epilepsy, substantial evidence is not yet available in this population, as noted by the applicant.

The technology is currently funded by MBS in Australia for other clinical indications (treatment of Parkinson's disease where the patient's response to medical therapy is not sustained and is accompanied by unacceptable motor fluctuations, or for treatment of essential tremor or dystonia where the patient's symptoms cause severe disability).

PASC confirmed that the proposed intervention is deep brain stimulation (DBS) of the anterior nuclei of the thalamus.

The DBS procedure consists of three main steps:

1. Preoperative planning

Preoperative planning includes presurgical testing to determine whether a patient will benefit from DBS therapy. Testing is performed in an outpatient setting or after admission to an epilepsy monitoring unit at a Comprehensive Epilepsy Program. VEEG monitoring, MRI, PET, and other imaging tests, as well as neuropsychology testing may be undertaken. A key activity prior to surgery is obtaining stereotactic coordinates for the target brain region by merging MRI data of the patient's brain with information from a brain atlas (Gionfriddo et al., 2013).

2. Surgical implantation

Implantation of the DBS system involves two steps. The first is placement of the stimulating electrode in the brain and the second step involves surgical placement of a small pacemaker-like device, or neurostimulator, under the skin in the chest. These steps are often performed in a single procedure. Surgery involves a multidisciplinary team of surgeons, epileptologists, theatre, and technical device staff.

Surgery requires shaving part or all of the patient's head, and the use of a fixed frame that surrounds the patient's head entirely or use of newer frameless systems which provide increased patient comfort and shorter operating times (Roth et al., 2018). Under either local or general anaesthesia, a neurosurgeon determines the exact placement and trajectory path for the electrode lead before burr holes are drilled into the skull at the planned electrode entry points. Functional landmark region-specific neuronal activity is used to confirm the target implantation region/structure during the surgical procedure. Under imaging guidance, one or more permanent microelectrodes are inserted into the brain and intraoperative fluoroscopy and postoperative MRI or computed tomography (CT) scans are obtained to confirm electrode placement. The leads are then connected to wires called lead extenders, which are tunnelled subcutaneously behind the ear, down the side of the neck, to below the clavicle, where they are attached to the neurostimulator (pulse generator) (Zangiabadi et al., 2019).

Part two of the surgery involves placement of the neurostimulator, which is often implanted on the same day/time as placement of the leads in the brain. Under general anaesthesia, the surgeon places the neurostimulator under the skin of the chest just below the collarbone and then connects the leads to the neurostimulator. The neurostimulator device is similar to a heart pacemaker and contains a small battery and a computer chip programmed to send electrical impulses to the brain via the implanted electrodes.

Depending on the person's surgical plan, people typically spend a day or two in hospital. Analgesia is prescribed to manage pain at the incision sites and overall healing usually takes several weeks.

3. Post-operative assessment

Over a three-to-six-month period, several postoperative outpatient clinic visits are arranged to program the neurostimulator system and determine optimal parameters including amplitude, frequency, and pulse width (Edwards et al., 2017). At the first visit several weeks after surgery, the stimulator is programmed by a clinician using a small hand-held computer that sets the amount (strength and length of time) of electrical stimulation given. These details are fine-tuned at subsequent visits using patient feedback and seizure control information. Precise settings vary from person to person, and it can take several months to find the right level of stimulation. Throughout this time the person's progress is closely monitored by their medical team. Patients are given their own programming device about the size of a mobile phone, enabling them to manage the neurostimulator themselves. When a person experiences a seizure and feels that further seizure(s) are likely, they can use their programmer to activate DBS therapy to try to stop a seizure from happening.

DBS would add a new treatment option for patients with severe drug-resistant epilepsy who were evaluated for surgical treatment within the Comprehensive Epilepsy Program, but are found ineligible for curative resective surgery.

PASC noted that patients eligible for DBS would be required to undergo a range of tests (i.e. EEGs, MRIs, consultations, laboratory tests) while being assessed for surgical treatment options in one of the 11 Comprehensive Epilepsy Program centres available in Australia. DBS would only be offered as an alternative

treatment option if the Comprehensive Epilepsy Program workup concludes surgery is not the most appropriate treatment, or when a patient continues to experience seizures despite surgical treatment.

PASC noted that Comprehensive Epilepsy Program centres currently do not exist in Tasmania, ACT and NT, and that there are significant barriers and bottlenecks regarding access to the Comprehensive Epilepsy Program. While telehealth services have recently somewhat improved access for patients from rural and remote Australia for follow-up appointments, the initial Comprehensive Epilepsy Program workup, which is very resource-intensive and takes 1-2 weeks, needs to be conducted in-person in inpatient settings.

The proposed medical service relies on a medical device/prosthesis. The DBS prostheses available for other indications in Australia may be used for the proposed service. Table 2 lists the components of Percept™ PC, a DBS implantable pulse generator manufactured by Medtronic Inc. and sponsored in Australia by Medtronic Australasia Pty Ltd. Several manufacturers have DBS devices in the Australian marketplace (Abbott, Boston Scientific Pty Ltd), however, these manufacturers do not have the Australian Register of Therapeutic Goods (ARTG) certificates with indications for epilepsy.

Table 2 Components of PERCEPT PC, DBS implantable pulse generator

Trade/Clinical Name	Model number	Description	ARTG Certificate	Billing Code	Benefit per unit	Quantity needed
Percept PC Brainsense	B35200	Implantable pulse generator	351630	MI401	$13,592	1
StimLoc	924256	Bur hole cover	151095	MC767	$497	2
Model 3387 Lead	3387-xx	Leads that are implanted into the brain	137374	MC244	$3,746	2
Lead Extension Kit models: 37086	37086xx	Accessory that connects the DBS Leads to the IPG	239412	MC852	$1,895	2
TH91D Kit:	TH91D02	A patient controller that allows patient to control stimulation settings	351590	MI400	$1,264	1
Tunneller	3755-40	Accessory to tunnel DBS Extensions from head to chest/abdomen	121281	MI003	$158	1
MER Cable	FC1020	Accessory to connect microelectrode to recording amplifier			$181	1
MER Canula / Microtargeting Insertion Tube	FC1036	Accessory to allow MER electrode and DBS lead to reach desired target			$158	1
MER Electrode	FC2002	Accessory that records brain activity and transmits to amplifier via MER cable			$1,354	1

ARTG=Australian Register of Therapeutic Goods; DBS=deep brain stimulation

Table 3 lists the consumables used as part of the service.

Table 3 Consumables used as part of the DBS medical service

Item	ARTG number	Description	Size
Medtronic DBS Tunnelling Tool Accessory Kit	121281	DBS Tunnelling Tool Accessory Kit	One size only
Medtronic MicroTargeting Electrodes	133619	Microelectrodes used for intra-operative recording of neuronal activity for DBS	Various
Microelectrode Cable	138186	Cable used for intracranial recording of neural activity prior to DBS	One size
Electrode Insertion Tube set	212222	Electrode Insertion Tube Set for DBS	One size only
Medtronic Screening Cable (Twist Lock)	119991	Screening Cable with Twist Lock for Intraoperative testing	One size only
Medtronic Screening Cable (Alligator Clip)	119991	Screening Cable with Alligator Clip for Intraoperative testing	One size only
Medtronic Accessory Kit for Deep Brain Stimulation	240576	Boots accessory kit for DBS (3550-25)	N/A

ARTG=Australian Register of Therapeutic Goods; DBS=deep brain stimulation; N/A=not applicable

PASC discussed several technical issues regarding externally rechargeable batteries for the DBS device, responsive neurostimulators, self-management options by the patient, and the user-friendliness of the DBS devices for the affected population. It was noted that current batteries last around five years, needing a replacement thereafter. The industry is moving towards rechargeable devices, lasting up to 10-15 years, with daily or weekly recharging requirements, however, this may not be suitable for patients with significant disabilities, e.g., intellectual disability. Responsive neurostimulators are currently not available in the Australian marketplace, however, they are available overseas.

PASC confirmed that it is unlikely that a repeat DBS intervention would be required. A potential need to reposition the lead has been reduced thanks to the advances in MRI stereotaxis used during implantation. One expert noted that in a recent study involving 20 patients, no repositioning was required. However, in rare cases repositioning or replacement of a damaged lead may be required.

Comparator(s)

VNS is as an appropriate comparator for DBS for epilepsy. Regulatory approval was granted in 2000 and VNS is listed on the MBS. Like DBS, VNS is a neuromodulation option and provides a palliative non-pharmacological alternative and/or adjunct therapy for management of seizures. VNS is not curative. While VNS is the closest comparator, there is robust multicentre evidence that DBS remains effective even if patients have not benefited from VNS.

A recent review concluded that VNS appeared to be an appropriate treatment option for a small number of adults and children with severe epilepsy whose disease is not adequately controlled with other available pharmacological and non-pharmacological treatments. VNS was deemed particularly useful for patients not responsive to, or suitable for, surgical resection of seizure foci (Shaw et al., 2020).

The mechanism of action of VNS is not understood, although it is assumed to involve neuro-modulatory action via the vagus nerve. VNS prevents seizures by sending regular, mild pulses of electric signals to specific brain structures via the vagus nerve, resulting in a reduction in the frequency and intensity of seizures and changes in mood, behaviour, and cognition (Panebianco et al., 2015).

VNS involves implantation of a vagus nerve stimulator (a pulse generator) under the skin on the left side of the chest. A wire from the device is then wound around the vagus nerve on the left side of the neck. The device produces repeating, low-level pulses of electrical current that are transmitted via electrical leads

along the vagus nerve that are propagated to the brainstem (Morris et al., 2013). The left vagus nerve is used to minimize adverse effects (Giordano et al., 2017).

Surgical adverse events (infection, vocal cord paresis) and stimulation side effects (hoarseness, voice change, cough) have been reported following VNS (González et al., 2019). Minor side effects (coughing, voice alteration) are often temporary and usually decrease over time. Adverse events can be minimized through adjustment of the stimulation parameters and are more likely to occur on high stimulation settings than low settings (Panebianco et al., 2015). If the VNS equipment or its components fail, people can be exposed to rare but serious harms (Shaw et al., 2020). As DBS is administering stimulation directly to the brain, it is not associated with many of the listed adverse effects that are associated with VNS.

A review of the 30-day risk profile for 77 adults undergoing VNS using multicentre patient data from an international database over 2005-2016 reported a mean operative time of 81.7 minutes and an average hospital stay of 0.27 days. Most (87.0%) patients were discharged on the day of operation. Low readmission (6.2%), reoperation (1.3%), and postoperative infection (1.3%) rates were reported (Selner et al., 2019). A systematic review of 78 studies (2,869 patients) and VNS registry data (5,554 patients) reported that around 60% of patients achieved a ≥50% seizure reduction after 2–4 years, with a seizure-freedom rate of 8% (Englot et al., 2016).

There are several important issues when considering VNS procedures. VNS creates safety issues for subsequent imaging, primarily due to patient safety concerns from lead heating in the MRI environment (Shellock et al., 2006). This means that many advanced imaging sequences are not able to be used for patients who have VNS leads in situ, limiting the ability to detect subtle, surgically amenable lesions in the future. Inability to access appropriate imaging may also impact on the accurate targeting of thalamic nuclei, which is aided by specific high quality MRI sequences, some of which are unsafe in the presence of VNS electrodes. Consequently, for safety reasons, a modified protocol needs to be followed when performing MRI brain scans in patients with VNS implanted (de Jonge et al., 2014). Where VNS does not work, it is not easy to remove the electrode wires without damaging the vagus nerve. A review of 497 VNS procedures for 247 primary VNS implantations over a 25-year period (mean follow up 12 years) reported that hematoma, infection, and vocal cord palsy were the most common complications postoperatively (rate approx. 2%). It was noted that these complications may cause major suffering and even be life threatening (Révész et al., 2016).

PASC confirmed that the proposed comparators, vagal nerve stimulation (VNS) or optimised medical treatment/best supportive therapy, are appropriate.

It was noted that VNS has many potential complications and that once the electrodes are positioned around the vagus nerve, it is very difficult to remove safely.

Healthcare resources delivered with VNS

The surgical placement of the VNS device and its components requires utilisation of the following healthcare resources:

- Surgical placement of the electrical pulse generator; also, possible surgical repositioning and/or removal of the electric pulse generator (requires: surgery, anaesthesia medications, anaesthetist fees, surgical fees, etc.)
- Surgical placement of VNS lead; also, possible surgical repositioning and/or removal of lead (requires: surgery, anaesthesia medications, anaesthetist fees, surgical fees etc.)

- Electrical analysis and programming of VNS device (electric pulse generator) using an external wand (requires: outpatient clinic visits, wand device).

PASC noted that VNS also requires resource-intensive assessment in a Comprehensive Epilepsy Program centre prior to implantation and therefore experiences similar barriers and bottlenecks as the proposed intervention (DBS).

It was noted that optimised medical therapy also carries significant financial costs, and offers relief to a very small proportion of patients once several antiepileptic medications have failed.

Several Medicare Benefits Schedule (MBS) item numbers cover VNS for epilepsy as described below:

Category 3 – THERAPEUTIC PROCEDURES
MBS item 40701 Vagus nerve stimulation therapy through stimulation of the left vagus nerve, subcutaneous placement of electrical pulse generator, for: (a) management of refractory generalised epilepsy; or (b) treatment of refractory focal epilepsy not suitable for resective epilepsy surgery Multiple Operation Rule (Anaes.) (Assist.)
Fee: $354.40 Benefit: 75% = $265.80

Category 3 – THERAPEUTIC PROCEDURES
MBS item 40702 Vagus nerve stimulation therapy through stimulation of the left vagus nerve, surgical repositioning or removal of electrical pulse generator inserted for: (a) management of refractory generalised epilepsy; or (b) treatment of refractory focal epilepsy not suitable for resective epilepsy surgery Multiple Operation Rule (Anaes.) (Assist.)
Fee**:** $165.90 Benefit: 75% = $124.45

Category 3 – THERAPEUTIC PROCEDURES
MBS item 40704 Vagus nerve stimulation therapy through stimulation of the left vagus nerve, surgical placement of lead, including connection of lead to left vagus nerve and intra-operative test stimulation, for: (a) management of refractory generalised epilepsy; or (b) treatment of refractory focal epilepsy not suitable for resective epilepsy surgery Multiple Operation Rule (Anaes.) (Assist.)
Fee: $701.45 Benefit: 75% = $526.10

Category 3 – THERAPEUTIC PROCEDURES
MBS item 40705 Vagus nerve stimulation therapy through stimulation of the left vagus nerve, surgical repositioning or removal of lead attached to left vagus nerve for: (a) management of refractory generalised epilepsy; or (b) treatment of refractory focal epilepsy not suitable for resective epilepsy surgery Multiple Operation Rule (Anaes.) (Assist.)
Fee: $629.90 Benefit: 75% = $472.45

Category 3 – THERAPEUTIC PROCEDURES
MBS item 40707 Vagus nerve stimulation therapy through stimulation of the left vagus nerve, electrical analysis and programming of vagus nerve stimulation therapy device using external wand, for: (a) management of refractory generalised epilepsy; or (b) treatment of refractory focal epilepsy not suitable for resective epilepsy surgery Multiple Operation Rule (Anaes.) (Assist.)
Fee: $197.40 Benefit: 75% = $148.05 85% = $167.80

Category 3 – THERAPEUTIC PROCEDURES
MBS item 40708 Vagus nerve stimulation therapy through stimulation of the left vagus nerve, surgical replacement of battery in electrical pulse generator inserted for: (a) management of refractory generalised epilepsy; or (b) treating refractory focal epilepsy not suitable for resective epilepsy surgery Multiple Operation Rule (Anaes.) (Assist.)
Fee: $354.40 Benefit: 75% = $265.80

The proposed medical service (DBS) is intended for use instead of VNS (i.e., it is a replacement or alternative). DBS and VNS are both established methods of providing neuromodulation in order to reduce seizure frequency and severity in patients with drug-resistant epilepsy who are not suitable for curative resective surgery. Deciding between DBS and VNS requires highly trained expert opinion from qualified neurosurgeons and epilepsy neurologists practicing in a Comprehensive Epilepsy Program. This decision is based on a complex discussion, taking into account patient factors such as seizure type and epilepsy syndrome, neuroimaging features, electrographic characteristics, and up-to-date knowledge of the literature. Within this difficult-to-treat cohort, there are patients that will benefit from DBS rather than VNS (i.e., DBS as an alternative to VNS).

The applicant claims that having VNS as a pre-requisite to DBS (i.e., as an add-on service) places patients at risk of harm. If less than optimal therapy is provided for a given patient, that patient may not achieve as

significant reductions in seizures, or may take longer to achieve that reduction. For a patient with drug-resistant epilepsy, this would infer a suboptimal reduction in harms or prolonged exposure to such harms. These harms have been previously outlined, and include injury, hospitalisation, and SUDEP. The applicant claims that DBS has been repeatedly proven to provide significant seizure reduction in patients that have previously failed VNS. In addition, this effect was no different in magnitude or significance, compared to patients that had not previously had VNS (i.e., neuromodulation-naïve). VNS is also more complicated to remove than DBS.

It is anticipated that DBS will be approved for use in patients with drug-resistant epilepsy that have not responded to antiepileptic medications and who are not candidates for VNS and/or who have failed a trial of VNS. Therefore, DBS would be considered as a substitute for VNS in most cases, except where DBS may potentially be used in addition to VNS not as an add-on service, but as a new service to be delivered in the future, after an unsuccessful trial of VNS.

PASC discussed the possibility of adding an alternative comparator of corpus callosotomy, a disconnection procedure (cutting the main fibre bundle connecting the two halves of the brain), for patients with generalised seizures. The applicant confirmed that there were no curative procedures for patients with drug-resistant generalised epilepsy. The experts noted that callosotomy was not a meaningful comparator and it was not commonly performed in Australia due to its destructive and irreversible nature. The procedure is reserved for a very small population of highly impaired young patients who typically suffer from a particular seizure type, atonic seizures (also known as drop attacks). In these patients, the main aim of corpus callosotomy is to reduce injuries resulting from falls caused by the drop attacks.

Outcomes

Safety outcomes

- Serious adverse events (neurologic and physical)
- Procedure related adverse events e.g., haemorrhage, implantations site infection
- Adverse events/complications e.g., depression, memory impairment.

Clinical effectiveness outcomes

Major (primary) outcomes:

- Reductions in seizure frequency and severity, including seizure-free days/months and proportion of patients with a 50% seizure reduction
- Improvements in Quality of Life/Activities of daily living - measured using an appropriate tool e.g., Washington Psychosocial Seizure Inventory, the Social Effects Scale, the Epilepsy Surgery Inventory, and the Quality of Life in Epilepsy Inventory (QOLIE), and the Liverpool QOL Battery, Liverpool Seizure Severity Scale (LSSS), Epilepsy Risk Awareness Scale (ERA), Generalised Anxiety Disorder Scale-7 (GAD-7), GASE (global assessment of severity of epilepsy- 7-point scale).

Secondary outcomes:

- Decrease in sudden death from epilepsy (SUDEP)
- Decrease in seizure-related injuries
- Decrease in hospital admissions for seizure-related injuries
- Decrease in carers' stress.

PASC confirmed the listed outcomes. DBS is rarely a curative procedure, but rather aims to reduce the number and severity of seizures.

PASC noted that not all patients will have the same adverse effects stemming from the implantation procedure and may develop unique side effects related to electrode placement.

PASC noted that out-of-pocket costs for medication and productivity losses for both patients and their carers as well as unmeasured costs of impact of the condition on occupation and relationships are significant, but currently not captured in the MSAC evaluation matrix.

Clinical management algorithms

The diagram in Figure 1 summarises the current clinical management pathway for people diagnosed with drug-resistant epilepsy.

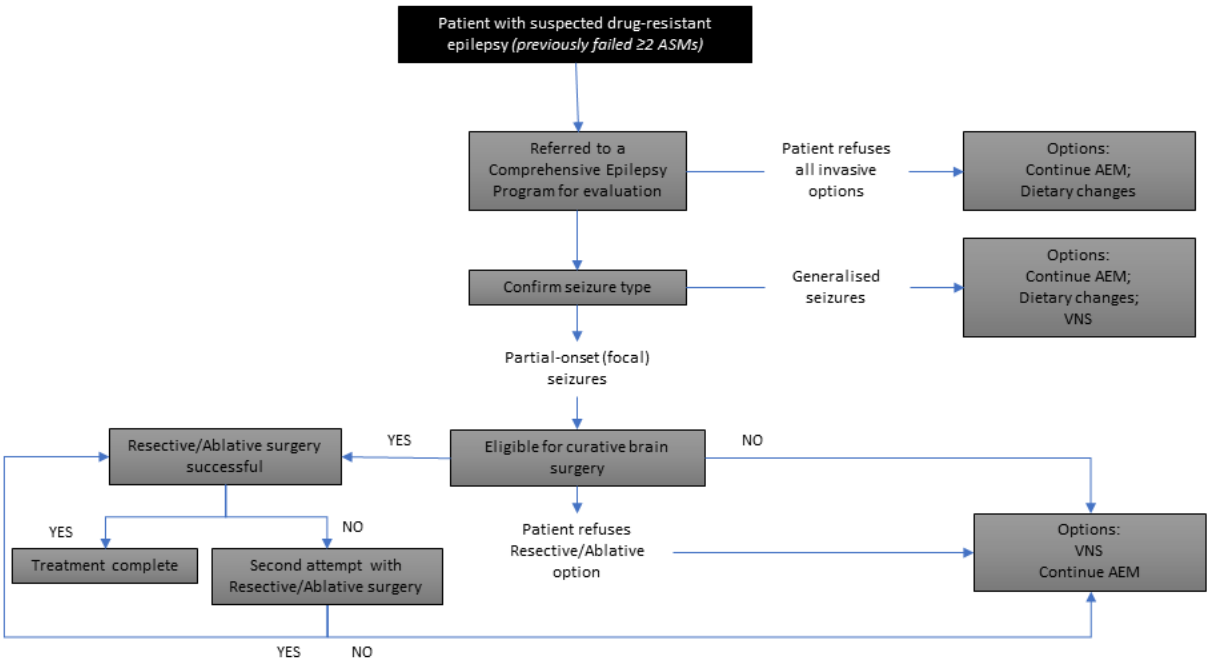

Figure 1 Current clinical management algorithm

AEM=antiepileptic medication; VNS=vagus nerve stimulation

The diagram in Figure 2 represents the clinical management pathway (algorithm) that patients would follow after the proposed service/technology is introduced. After the introduction of the proposed new therapy (DBS), people with drug-resistant epilepsy would have an additional MBS-approved treatment option, in addition to brain surgery and VNS.

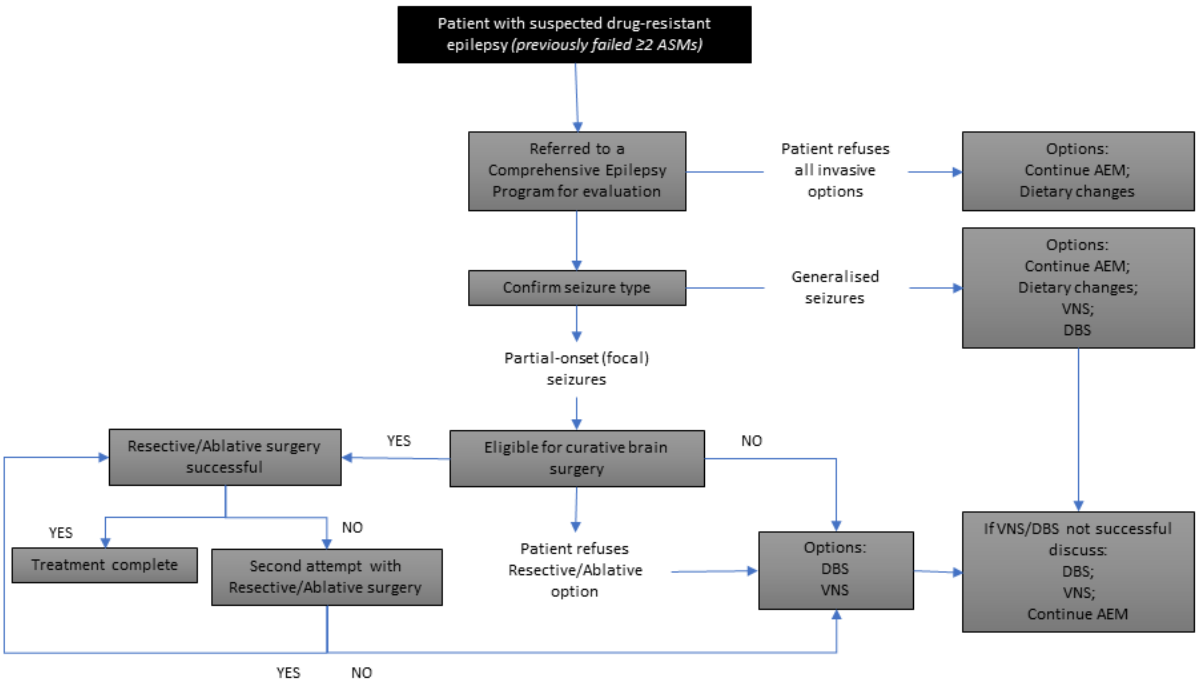

Figure 2 Proposed clinical management algorithm

AEM=antiepileptic medication; DBS=deep brain stimulation; VNS=vagus nerve stimulation

PASC noted that the clinical management algorithms are appropriate. The difference between the current and proposed management algorithm is the addition of DBS as a treatment option.

Proposed economic evaluation

The overall clinical aim of DBS therapy is to reduce the frequency and severity of epileptic seizures and improve quality of life in patients with drug-resistant epilepsy, who have considered and/or trialled other pharmacological and surgical approaches without success.

Based on this clinical claim of superior clinical effectiveness and non-inferior safety of DBS for treatment of drug-resistant epilepsy compared to VNS, the appropriate economic evaluation is cost-effectiveness or cost-utility analysis (Table 4).

Table 4 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	Uncertain[a]	Noninferior[b]	Superior
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain[a]	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior[b]	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis

? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis

[a] 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations

[b] An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

PASC confirmed that a cost effectiveness analysis (CEA) or cost utility analysis (CUA) is appropriate given the clinical claims of superior clinical effectiveness and non-inferior safety compared with VNS.

The applicant confirmed that for the additional second comparator of optimised medical/best supportive care, the clinical claim would be of superiority of DBS for both clinical effectiveness and safety.

It should be noted that the application does not reference any comparative evidence to support the clinical claim. Scoping searches performed by the Assessment Group also did not identify any relevant comparative evidence. In a pre-PASC meeting, the applicant confirmed they were not aware of any direct comparative evidence for VNS *versus* DBS for treatment of drug-resistant epilepsy, and that it was unlikely such trials would be conducted in the future considering the clinical profiles of DBS and VNS.

Proposal for public funding

The applicant proposed an amendment to the patient population under existing MBS items for DBS (items 40851, 40852, 40854, 40856, 40858, 40860, 40862). The aim is to expand current MBS items for DBS to include the subgroup of people with epilepsy who have been evaluated at a Comprehensive Epilepsy Program and have been determined to have drug-resistant epilepsy and who are not suitable for resective surgery. No changes have been proposed to the existing fees.

PASC noted that the proposal is to amend MBS item descriptors presently used for DBS for essential tremor and other conditions. The proposed addition of conditions eligible for the procedure reads 'drug-resistant epilepsy in patients not suitable for resective surgery following assessment by a Comprehensive Epilepsy Program'.

PASC noted that the proposed procedure is bilateral and queried whether amendment to unilateral MBS items was needed. The applicant argued that unilateral procedures may still be necessary as about 10% of patients may need re-intervention for a unilateral lead or electrode failure; PASC agreed with the justification.

Category 3 – THERAPEUTIC PROCEDURES
MBS item 40851 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: 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* *Drug-resistant epilepsy in patients not suitable for resective surgery following assessment by a Comprehensive Epilepsy Program.* Multiple Operation Rule (Anaes.) (Assist.)
Fee: $4,123.60 Benefit: 75% = $3,092.70

Note: Proposed changes to the current MBS item descriptors are marked in blude italics. Edits to the proposed MBS item descriptors by the Assessment group based on current MBS item descriptors are marked in red.

Category 3 – THERAPEUTIC PROCEDURES
MBS item 40852 Proposed item descriptor: DEEP BRAIN STIMULATION (unilateral) subcutaneous placement 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* *Drug-resistant epilepsy in patients not suitable for resective surgery following assessment by a Comprehensive Epilepsy Program.* Multiple Operation Rule (Anaes.) (Assist.)
Fee: $354.40 Benefit: 75% = $265.80

Note: Proposed changes to the current MBS item descriptors are marked in blude italics. Edits to the proposed MBS item descriptors by the Assessment group based on current MBS item descriptors are marked in red.

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* *Drug-resistant epilepsy in patients not suitable for resective surgery following assessment by a Comprehensive Epilepsy Program.* Multiple Operation Rule (Anaes.) (Assist.)
Fee: $547.70 Benefit: 75% = $410.80

Note: Proposed changes to the current MBS item descriptors are marked in blude italics. Edits to the proposed MBS item descriptors by the Assessment group based on current MBS item descriptors are marked in red.

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* *Drug-resistant epilepsy in patients not suitable for resective surgery following assessment by a Comprehensive Epilepsy Program.* Multiple Operation Rule (Anaes.) (Assist.)
Fee: $265.80 Benefit: 75% = $199.35

Note: Proposed changes to the current MBS item descriptors are marked in blude italics. Edits to the proposed MBS item descriptors by the Assessment group based on current MBS item descriptors are marked in red.

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* *Drug-resistant epilepsy in patients not suitable for resective surgery following assessment by a Comprehensive Epilepsy Program.* Multiple Operation Rule (Anaes.) (Assist.)
Fee: $547.70 Benefit: 75% = $410.80

Note: Proposed changes to the current MBS item descriptors are marked in blude italics. Edits to the proposed MBS item descriptors by the Assessment group based on current MBS item descriptors are marked in red.

Category 3 – THERAPEUTIC PROCEDURES
MBS item 40860 DEEP BRAIN STIMULATION (unilateral) target localisation incorporating anatomical and physiological techniques, including intra-operative 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* *Drug-resistant epilepsy in patients not suitable for resective surgery following assessment by a Comprehensive Epilepsy Program.* Multiple Operation Rule (Anaes.) (Assist.)
Fee: $2,104.65 Benefit: 75% = $1,578.50

Note: Proposed changes to the current MBS item descriptors are marked in blude italics. Edits to the proposed MBS item descriptors by the Assessment group based on current MBS item descriptors are marked in red.

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* *Drug-resistant epilepsy in patients not suitable for resective surgery following assessment by a Comprehensive Epilepsy Program.* Multiple Operation Rule (Anaes.) (Assist.)
Fee: $197.40 Benefit: 75% = $148.05 85% = $167.80

Note: Proposed changes to the current MBS item descriptors are marked in blude italics. Edits to the proposed MBS item descriptors by the Assessment group based on current MBS item descriptors are marked in red.

Of note, a new MBS item for remote programming of DBS neurostimulator pulse generator (MBS item 40863) will be implemented on 1 November 2022. An amendment to this item to include drug-resistant epilepsy may be considered once implemented.

DBS for epilepsy will be delivered by specialist neurosurgeons (Fellows of the Royal Australasian College of Surgery (FRACS) with specialist training in neurosurgery and expertise in functional neurosurgery) and specialist neurologists with advanced training in epilepsy or working in an advanced Comprehensive Epilepsy Program, with experience in neuromodulation. It is anticipated that general practitioners, neurologists, and possibly other medical specialists will refer patients to neurosurgeons for discussion/consideration of DBS for epilepsy. DBS therapy for epilepsy will not be delegated or referred to another health professional for delivery. Consequently, the proposed service should only be rebated by the health professional billing the service.

DBS for epilepsy would only be provided in hospital inpatient setting (public or private hospitals).

DBS surgery would be performed once in the patient's lifetime.

Programming would occur four times per year in the first year and possibly once or twice a year thereafter for maintenance.

Battery replacement would occur about once every five years.

While DBS surgery is a life-long surgery, new DBS device components may be required over a patient's lifetime where therapy is successful. The time interval for revision surgery will vary amongst patients. A major determinant for the frequency of repeat procedures will be the battery life of the neurostimulator device implanted. The neurostimulator box may need to be changed on average every five years, or less often, depending on the type of device used and how often the device is used by the individual.

For example, in DBS for Parkinson's disease, the frequency of device replacement is dependent on the model of neurostimulator, and the program settings used. The Percept™ PC neurostimulator battery lasts over 3 to 5 years on average.

Electrode lead revision surgery in the context of Parkinson's DBS is around 10% of cases in Australia. An Australian cross-sectional, population-based study assessed data from the Australian Government covering a 15-year period (2002-2016) for 1849 patients with Parkinson's disease following DBS implantation. Annual programming rates of 6.9 in the first year, and 2.8 in subsequent years, were reported in this cohort (Xu et al., 2021).

Device performance and battery life are important considerations. DBS device performance, including the battery level, is assessed at each medical review by the person's doctor. Patients can also check battery performance using their patient programmer at any time and are instructed to contact their doctor if they stop receiving symptom relief. Patients are advised to plan to have their device replaced, rather than waiting for their battery to run out (Medtronic United Kingdom).

DBS surgery usually takes around four hours to perform (expert opinion). The likely cost of providing the medical service will be made up of the fee for surgical implantation of the device and leads and the inpatient hospital admission costs. A funding stream will also be required for the purchase of the neurostimulator device and associated components, including the leads and the patient handheld controlling device. The breakdown of MBS fees is described in terms of neurosurgery and neurology

components for implantation of the device. The MBS items supporting DBS for epilepsy would be restricted for use by neurosurgeons.

An overall breakdown of delivery of DBS is presented in Table 5. Summary of prosthesis and single-use consumables' costs is presented in Table 6.

Table 5 Approximate cost profile of DBS for epilepsy

Item	Cost	Reference
Neurosurgeon	$4,123.60	MBS item number 40851
Neurologist	$2,104.65 $197.40	MBS item number 40860 MBS item number 40862
Prostheses/single use consumables	$28,983.01 (total)	Please refer to Table 6 for details
Anaesthesia	Variable depending on individual patient needs & surgical plan	Anaesthesia
Hospital admission (including investigations)	Variable depending on hospital (public/private)	Hospital admission (including investigations)

MBS=Medical Benefits Schedule

Table 6 Summary of prostheses/single-use consumables

Model No.	Description	Quantity	Unit Prices AUD	Total Price AUD
924256	StimLoc caps	2	$497	$994
FC1020	MER Cable	1	$181	$181
FC1036	MER Canula	1	$158	$158
FC2002	MER Electrode	1	$1354	$1,354
3387-40	DBS Lead	2	$3,746	$7,492
3755-40	DBS Tunneller	1	$158	$158
37086xx	DBS Extension	2	$1,895	$3,790
B35200	Percept IPG – PC	1	$13,592	$13,592
924256	StimLoc caps	2	$497	$994
FC1020	MER Cable	1	$181	$181
Total				**$28,983.01**

Healthcare resources and medical services that would need to be delivered at the same time as DBS implantation include:

- Anaesthesia medications
- Analgesia medications
- MRI—scan of head (including MRA, if performed) for epilepsy (R) (Anaes.) (Contrast) – MBS Item 63061 (after fitting a stereotactic frame, neuroimaging is used intraoperatively to map the brain and identify the areas in the brain where the electrodes will be placed)
- Preoperative and postoperative CT scan – MBS Item 56001.

Category Category 5 - DIAGNOSTIC IMAGING SERVICES
MBS item 63061 MRI—scan of head (including MRA, if performed) for epilepsy (R) (Anaes.) (Contrast) Bulk bill incentive (Anaes.) (See para IN.0.19 of explanatory notes to this Category)
Fee: $403.20 Benefit: 75% = $302.40 85% = $342.75

Category Category 5 - DIAGNOSTIC IMAGING SERVICES
MBS item 56001 Computed tomography—scan of brain without intravenous contrast medium, not being a service to which item 57001 applies (R) (Anaes.) Bulk bill incentive (See para IN.0.19 of explanatory notes to this Category)
Fee: $199.80 Benefit: 75% = $149.85 85% = $169.85

It is estimated that approximately 30 patients will utilise DBS in the first year.

It is estimated that DBS uptake will increase by approximately 20% per year, until a steady state is reached. The demand for DBS surgery is expected to plateau at three to five years following availability of the DBS on the MBS.

Potential barriers to uptake of DBS include access/referral to a Comprehensive Epilepsy Program for evaluation of suspected drug-resistant epilepsy. Other barriers include access to hospital beds in the public hospital system and access to, and availability of, the device and components to enable surgery in the public hospital system. Medical workforce would be a significant limiting factor, with a small number of specialist neurosurgeons adequately trained to insert a DBS device, and an equally small number of epilepsy neurologists with sufficient experience in neuromodulation.

The applicant claims that ‘leakage’ of DBS to other patient populations is not anticipated, as several MBS items already exist for conditions where DBS is widely accepted to have proven benefits. This includes current MBS listings for DBS in Parkinson's disease, where the patient's response to medical therapy is not sustained and is accompanied by unacceptable motor fluctuations, as well as in essential tremor or dystonia where the patient's symptoms cause severe disability. ‘Leakage’ to other population groups is also claimed to be unlikely due to the fact that there is a paucity of evidence to support DBS in non-research settings. For example, DBS has not received FDA regulatory approval for use in depression, bipolar disorder or for treating Tourette syndrome in the United States.

Summary of public consultation input

Consultation feedback was received from two [2] professional organisations and one [1] consumer organisations:

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

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

Clinical need and public health significance

The main benefits of public funding received in the consultation feedback included:

- Improved seizure control and increased patient independence, quality of life and employability
- Reduced background antiepileptic medication dosing
- Few side effects once immediate perioperative issues have settled, with benefits building up overtime
- Reduced hospital admissions for recurrent seizures
- Reduced carer stress.
- The consultation feedback noted that the main disadvantages related to the invasive nature of intervention and associated risk of infection, and the need to replace the stimulator box for non-rechargeable devices.

Other services identified in the consultation feedback as being needed to be delivered before or after the intervention included:

- Neurosurgical review before and after implantation
- MRI Brain pre-implantation
- Routine blood tests pre-surgically
- CT Brain pre and post-implantation to guide electrode implantation and check position of electrode contacts
- Neurologist reviews post-implantation for up-titration of stimulator settings
- Ongoing psychosocial support.

Indication(s) for the proposed medical service and clinical claim

- The consultation feedback ranged from' strongly agreeing' to 'agreeing' with the proposed population(s), the comparator and the clinical claim.
- The consultation feedback noted that the defined population is well defined and would ensure that patient suitability for DBS will be determined by professionals with expertise in intractable epilepsy.
- It was noted that DBS appears more effective and has fewer side effects than the proposed comparator, vagal nerve stimulation.

Cost information for the proposed medical service

- The consultation feedback ranged from 'strongly agreeing' to 'agreeing' with the proposed service descriptor and the proposed service fee.
- The MDSANZ sought clarification on whether unilateral programming for the proposed epilepsy indication is comparable to existing movement disorder indications, which are often asymmetrical and are individualised for optimal symptom control.

PASC noted that feedback was received from three organizations: a Foundation and two specialist groups. All were supportive of the proposed technology.

Next steps

PASC advised that, upon ratification of the post-PASC PICO, the application can proceed to the Evaluation Sub-Committee (ESC) stage of the MSAC process.

PASC noted the applicant has elected to progress its application as a DCAR (Department-Contracted Assessment Report). PASC advised the DCAR should include only the population with generalised seizures if there is sufficient evidence for its inclusion.

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