



Australian Government

Department of Health

RATIFIED PICO

Application 1614:

**Magnetic resonance-guided focused ultrasound for
the treatment of medically refractory essential tremor**

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

Component	Description
Patients	Adults with medically refractory ^a essential tremor [under the care of a neurologist] and symptoms causing severe [functional or social] disability
Intervention	Unilateral Magnetic resonance-guided focused ultrasound (MRgFUS) thalamotomy
Comparator	<ul style="list-style-type: none"> • Deep brain stimulation (DBS), unilateral or bilateral^b • Best supportive medical care (BSC)^c,
Outcomes	<ul style="list-style-type: none"> • Safety: <ul style="list-style-type: none"> ○ Adverse Events: <ul style="list-style-type: none"> ▪ Numbness, paraesthesiae, ataxia, dysarthria, dysphagia, in short and long term (> 12 months) ▪ Intraprocedural harms (due to helmet or other events as noted in RCT and observational studies) ▪ Failed procedure rate (skull thickness, claustrophobia/anxiety, other) • Efficacy / effectiveness including, but not limited to, patient-relevant outcomes: <ul style="list-style-type: none"> ○ Number of patients with benefit (number reaching minimum clinically important difference (MCID) threshold of tremor scale (if validated)) ○ Median (not mean) benefit in tremor, using MCID of CRST ○ Duration of adequate benefit (using MCID) ○ Need for retreatment with DBS ○ Ability to cease medications ○ QoL outcomes- standardised (SF36) and disease specific (QUEST) ○ Return to employment/productivity ○ Change in social disability • Healthcare resources. <ul style="list-style-type: none"> ○ Costs to deliver the intervention, including cost of the treatment kit^d ○ Re-intervention costs • Cost-effectiveness. • Total Australian Government healthcare costs. <ul style="list-style-type: none"> ○ Total cost to the Medicare Benefits Schedule (MBS) ○ Total cost to the Pharmaceutical Benefits Scheme (PBS) ○ Total cost to other healthcare services

^a Patients who fail to derive adequate benefit from pharmacological treatment (first-line treatment: propranolol or primidone; gabapentin, alprazolam and topiramate available where first-line drugs are contraindicated or not tolerated)

^b Patients might also be receiving concurrent medical therapy (i.e. BSC)

^c In those unwilling to accept the risks associated with DBS or are contra-indicated for the procedure

^d The applicant advised that the helmet is reused compared with the treatment kit which is disposable

POPULATION

Essential tremor (ET) is one of the most common movement disorders, affecting approximately 1% of the population worldwide (Louis and Ferreira 2010). It is a chronic, progressive neurologic disease whose identifying feature is a kinetic tremor, i.e. an involuntary rhythmic oscillatory movement of one or both arms that occurs during voluntary movements (writing, eating). The tremor cannot be attributed to another cause (e.g. Parkinson's disease). There is a slow progression of tremor intensity with age and the tremor may also spread to involve other body regions, most commonly the head, larynx (voice tremor), and lower limbs (Clark and Louis 2018). The cause of ET is unknown.

ET is heterogeneous in its clinical presentation, pharmacological response and disease progression, and is therefore increasingly considered as a syndrome of different clinical features rather than a single entity. The International Parkinson and Movement Disorder Society set the following criteria for diagnosis of ET (Bhatia, Bain et al. 2018):

- Isolated tremor syndrome characterised by bilateral upper-limb action tremor
- Duration of at least 3 years
- With or without tremor in other locations (e.g., head, voice, or lower limbs)
- Absence of other neurologic signs, such as dystonia, ataxia, and parkinsonism.

Depending on the symptom severity, persons living with ET may experience significant functional and psychological disability. The symptoms may interfere with the ability to perform activities of daily living (ADL) such as drinking, dressing, writing and drawing, and shaving. Patients may be forced to retire prematurely.

ET may also be associated with other neurological signs, such as cognitive and sensory impairments, mild ataxia, or impaired memory (Haubenberger and Hallett 2018). Patients may also develop sleep disturbances, depressive symptoms, and dementia. The gradually worsening tremor together with these co-morbidities result in a functional decline, as well as increased frailty.

ET is among the most prevalent movement disorders (Louis and Ferreira 2010), and increases markedly with age, and exponentially with advanced age (Louis 2019). A 2010 meta-analysis of population-based prevalence studies found worldwide prevalence to be 4.6% for ages ≥ 65 years, increasing to be as high as 22% for ages ≥ 95 years (Louis and Ferreira 2010). Despite this high prevalence, the precise number of cases of ET is difficult to determine, since the variable clinical presentation often leads to misdiagnosis. The application form provided prevalence estimates from the literature in Table 1. To date, no estimates are available for Australia.

Expert opinion provided in the application form estimated that of the Deep Brain Stimulation (DBS) procedures performed in Australia within a private hospital setting (Table 3) approximately 25% are used to treat severe disabling ET (N=65), with the remainder performed for Parkinson's disease or dystonia.

Table 1 Prevalence estimates of ET

Author	Year	Country	Study design	Ages	Prevalence estimate
Eliassen	2019	Denmark	Population-based screening followed by clinical examination in randomly selected subgroup	≥40 years	3.1%
Louis	2014	USA	Analysis of 3 population-based prevalence studies	Total population	2.2%
Bharucha	1988	India	Door to door, community-based survey	Total population	1.7%
Oh	2014	South Korea	Prospective cohort study	elderly persons ≥65 years	3.6%
Yao	2015	China	Epidemiological survey	≥45 years	3.6%
				≥75 years	4.3%
Dogu	2003	Turkey	Screening surveys and subsequent examinations with neurologists	≥40 years	4.0%
Seijo Martinez	2013	Spain	Door-to-door evaluations and subsequent neurological examinations	≥65 years	8.4%

Source: Table 3, p32 of the application form
ET = essential tremor

PASC noted that currently, there is no Australian prevalence data available to estimate the size of the proposed population, using an epidemiological approach. PASC noted the applicant estimated the population size using a market-share approach, but did not include the number of deep brain stimulation (DBS) procedures performed in public hospitals, which would underestimate the size of the proposed population. PASC considered that the utilisation estimates would need to be adequately explained in the assessment phase.

The applicant agreed that an estimation of utilisation of DBS for ET in the public hospital setting will be required and will be presented in the Applicant Developed Assessment Report.

Rationale

The point of entry for care is typically a general practitioner (GP), who makes a diagnosis or referral to a neurologist based on a comprehensive patient history review and neurologic examination. Routine laboratory testing to exclude abnormalities that can carry a predisposition to enhanced physiologic tremor should include thyrotropin, electrolyte levels, and liver and kidney function measurements (Haubenberger and Hallett 2018).

Where tremor affects ADL or quality of life, pharmacological treatment is offered to control the symptoms as a first-line treatment. The two most commonly used drugs for ET are propranolol and primidone (Haubenberger and Hallett 2018, Sharma and Pandey 2020). Medical therapy rarely achieves complete tremor control and according to Sharma and Pandey (2020), their mean efficacy is about 50% in terms of tremor. Drug tolerance occurs after chronic treatment, and 30-50% of patients may be completely resistant to first-line pharmacotherapy. When first-line drugs are contraindicated or not tolerated, second-line treatment includes topiramate, gabapentin, and alprazolam. Patients who fail to derive adequate benefit from pharmacological treatment and/or are intolerant to medical intervention are considered to have medically refractory ET.

Following failure to achieve an adequate response to pharmacological therapy, patients are typically referred to a neurologist within a movement disorder clinic for assessment of suitability for therapeutic interventions. After initial appraisal, patients may undergo an extensive work up to assess suitability for further treatment including surgery in a movement disorder clinic by a specialist

team, which includes a movement disorder neurologist and neurosurgeon. The team may also include other specialists such as a movement disorders nurse, neuropsychiatrist, and neuropsychologist, depending on the team's usual protocol. This process aims to determine the likely benefit and risks of performing each type of procedure on an individual basis. Treatment of medically refractory ET often includes persisting further with pharmacological therapy as described above (optimised medical therapy). DBS may also be considered in this difficult to treat population. At present, DBS is the only MBS reimbursed intervention for patients with medically refractory ET. The treatment is limited to patients whose symptoms cause severe disability. Patients contraindicated or not suitable for surgery are continued to be managed through best supportive care (BSC).

Magnetic resonance-guided focused ultrasound (MRgFUS) has been developed to assess whether ablative therapy may be beneficial for people with medically refractory ET, where the patient's symptoms cause severe disability. The applicant acknowledges that the definition of failure to derive adequate benefit to treatment is open to interpretation. There are currently no set guidelines that define the duration of treatment or thresholds of benefit when defining medically refractory ET. It should, however, be noted that the decision to undergo MRgFUS would not be undertaken lightly, and it is likely that most patients would trial a range of pharmacologic therapies before considering the procedure.

PASC confirmed the population as stated in the draft PICO. PASC queried whether 'medically refractory' should be defined in the proposed population and what duration is required before a patient is considered medically failed. PASC noted there are currently no set guidelines that define the duration of treatment or thresholds of benefit when defining 'medically refractory' but noted the pivotal trial (Elias et al. 2016) recruited patients with tremor that was refractory to at least two trials of medical therapy, including at least one first-line agent (propranolol or primidone).

The trial population in the pivotal RCT (Elias, Lipsman et al. 2016) included patients with ET, diagnosed by a neurologist specialising in movement disorders. It was noted the pivotal trial used the Clinical Rating Scale for Tremor (CRST) scores to recruit the trial population: patients were eligible if they had a postural or intention tremor of the hand that was moderate to severe (defined by a score of ≥ 2 on the CRST [scores range from 0 to 4 per component assessed, and higher scores indicate more severe tremor]) and disabling (defined by a score of ≥ 2 on any of the eight items in the disability subsection of the CRST [scores range from 0 to 4 per item, and higher scores indicate greater disability]). It should be noted that the use of the CRST score is one of the major flaws of the RCT, as it is a new scale and it is not clear what a minimum clinically important difference (MCID) would be and what difference in scale would correlate with patient improvement and satisfaction with treatment.

Additional eligibility criteria were: tremor that was refractory to at least two trials of medical therapy, including at least one first-line agent (propranolol or primidone); and, for patients receiving concurrent medical therapy, medication doses had to be stable for 30 days before randomisation. This means patients might also receive concurrent medical treatment alongside MRgFUS, as reflected in the algorithm (Figure 2).

Patients were excluded if they had a neurodegenerative condition, unstable cardiac disease, coagulopathy, risk factors for deep-vein thrombosis, severe depression (defined by a score ≥ 20 on Patient Health Questionnaire 9 [scores range from 0 to 27, with higher scores indicating more severe depression]), or cognitive impairment (defined by a score of < 24 on the Mini-Mental State

On the day of treatment, the patient's head is shaved, and a stereotactic frame is affixed to the skull under local anaesthetic. The patient is positioned on the treatment bed with his/her head secured to the phased-array ultrasound transducer (the Exablate Neuro helmet). Cold water is circulated around the scalp.

2. [Planning and target verification](#)

Intraoperative MRI images are taken and may be fused with pre-op images to plan the treatment and identify the target.

Prior to treatment, low energy sonications (application of ultrasound energy) are used to accurately pinpoint the target on the real-time MRI. Next, moderate level sonications allow assessment of patient response and any potential adverse effects before making the final lesion.

3. [Treatment](#)

The focused ultrasound treatment consists of up to 1024 ultrasound waves directed to the target in the VIM. At the focal point, temperatures increase to near 140°F/60°C, causing thermal ablation of the target tissue. The treatment is continuously guided by MRI for real-time thermal feedback of temperature changes (MR thermography) at the target, as well as non-focal temperature trends. The treatment is unilateral, generally treating the dominant hand.

Intraoperative and interactive patient assessment is done to correctly identify the anatomical target and intraoperative MRI images are taken to evaluate the lesion formation.

4. [Assessment](#)

Treatment outcome is confirmed through neurological assessments as well as using a post-treatment scan immediately post-procedure. In a successful procedure, patients may experience an immediate reduction in their tremor. They are admitted overnight for observation. They may return to normal activities the following day in the absence of complications.

Patients are required to undergo a post-operative MRI scan at 3 and/or 6 months follow up to assess lesion formation and dynamics. The post-operative MRI should be completed at around 3 months. Should the treating physician feel that a further follow up is required, an additional MRI may be requested at 6 months post-procedure.

A trained specialist is required to deliver the proposed service. A training plan devised by the applicant is attached to the application form. A movement disorder specialist present at the procedure will provide intraoperative clinical evaluation. The applicant proposes that there should not be any limitations on who will be able to deliver the proposed service, such that a radiologist, neurologist or neurosurgeon with adequate training may be able to perform more than one of these roles during the procedure.

The applicant notes that whilst the proposed MBS items identify tasks and MBS fees for the neurology, neurosurgery and radiology components of the procedure, it is feasible, and indeed probable, that over time (as physicians become more adept at executing the procedure) the tasks may be performed by, and fees reimbursed to, physicians of any of the three disciplines mentioned (radiology, neurology and neurosurgery). That is to say, the three item numbers proposed for the intraoperative component of MRgFUS will be performed and charged to the MBS by only two physicians performing the three components of the procedure.

The proposed medical service is not currently funded or reimbursed in the private or public setting in Australia for the same or another clinical indication. The TGA approved indication(s) is for malignant or benign tumours, or other disease conditions and is thus broader than the proposed population (for medically refractory ET). There are two ARTG listings for the device (260438, 128137).

The application form indicated that currently, only one centre in Australia offers MRgFUS for the treatment of medically refractory ET. Due to capital costs of the technology, it is anticipated that MRgFUS will be limited to only a very small number of centres, therefore potentially limiting access for some patients. The application form also identified additional supply side constraints, including availability of specialists to perform the procedure. *PASC noted that the intervention is complex and is only available at one centre in Australia, and that there would be significant equity of access issues.*

The Applicant noted, that since lodgement of the Application form, a second centre in Australia at the Future Medical Imaging Group Center in Melbourne has acquired the Exablate Neuro technology and is now treating ET patients with MRgFUS. While this has increased access, it is acknowledged that equity of access issues still remain. Access is expected to continue to improve over time as more hospitals take up the MRgFUS technology – especially if approved for funding on the MBS. PASC noted the applicant's advice which stated that a high proportion of the costs relate to service costs for capital and that out-of-pocket costs will be determined on the agreed MBS rebate.

Based on current MBS utilisation of DBS (Table 3), the application form estimated that demand for MRgFUS would be less than 100 patients per annum. It should be noted that this estimation of demand for the procedure might be very uncertain, because the utilisation data from the estimate cover private procedures only. Moreover, MRgFUS is considered less invasive than DBS, so the real patient population may be considerably larger.

The application form provided breakdown costs for delivery of the MRgFUS procedure (see Table 4 in Appendix A). The application form also indicated an intention to submit an application to the Prostheses List (Part C) for potential funding of the disposable patient kit.

PASC noted that the prosthesis cost (treatment kit) is likely to be substantial and not covered in detail in this application. PASC noted the applicant intended to submit an application to the Prostheses List (Part C) for potential funding of the disposable patient kit.

The applicant confirmed it will provide a detailed evaluation of cost, including for the prosthesis and service costs for capital, in the ADAR.

Rationale

In Australian clinical practice, MRgFUS is currently provided once on the dominant affected side as a unilateral treatment.

PASC confirmed the proposed intervention should be once-only treatment with unilateral MRgFUS thalamotomy.

PASC agreed with the applicant who advised that contralateral treatment is not relevant to this application, noting that contralateral treatment is currently considered investigational. However PASC noted, the application form (not the PICO) stated that the proposed service would first be delivered once per patient on the dominant side and that treatment of the contralateral side may be performed after a minimum of six months after successful treatment of the dominant side. Further,

PASC also noted that retreatment was uncommon and that the vast majority of patients are expected to only have one unilateral procedure on the basis that the majority of clinical benefits of treatment with MRgFUS are derived by treating the dominant side.

The applicant considered that treatment of the contralateral side is not irrelevant to this application. While the applicant considered that treatment of the contralateral side is currently investigational, the primary concern regarding contralateral treatment is with safety. It is argued that as the safety data supporting contralateral treatment transpires, patients should be able to access contralateral treatment if they so wish and are indicated for the procedure, at the discretion of the treating neurologist and neurosurgeon (noting that the number of patients seeking contralateral treatment is expected to be low given the benefits of treating the dominant side). Conversely, should the adverse event profile associated with contralateral MRgFUS appear to be unfavourable, treating physicians would simply not perform the procedure. Accordingly, the applicant was of the view that inclusion of the contralateral treatment in the item descriptor would be considered reasonable.

COMPARATOR

Patients who have failed treatment with pharmacotherapy and have functional limitations in everyday activities may be treated surgically, with lesional surgery or neuromodulation techniques (DBS). DBS is the most used surgical procedure for ET and the only reimbursed intervention for patients with medically refractory ET in Australia (Figure 1). DBS involves inserting a permanent electrode into the thalamus or other region causing tremor through a burr hole in the skull and electrically stimulating the VIM. Electrode stimulation is generated by an implantable neurostimulator (pacemaker box) located in the chest region and connected by a wire (Zaaroor, Sinai et al. 2018).

Following a DBS procedure, patients are transferred to the intensive care unit for overnight observation. A cerebral CT scan is performed post operatively as routine. In most patients, stimulation is commenced on the evening following surgery. Patients are transferred to the Neurosurgical Ward the following morning and required to stay in hospital for a minimum of one week.

Once discharged, patients are required to return to their treating neurologist frequently for several months in order to have the stimulation adjusted and optimised. Doctors must also supervise reductions in patients' medications. Similar to MRgFUS, patients might also receive BSC alongside DBS, as reflected in the algorithm (Figure 2). After a few months, the number of medical visits usually decreases significantly, though patients are still required to return to have their stimulator checked regularly for monitoring and adjustment of hardware settings. Complications that can arise requiring re-intervention include:

- Fracture or breakage of the wire or cable
- Battery failure (life span of the pulse generator battery is typically 3-5 years)
- Erosion of the cable or device through the skin
- Migration of the electrode in the brain due to failure of the anchor
- Infection at the implant site(s).

In Australian clinical practice, DBS is generally preferred over lesional surgery, as it can be reversed, it leaves little or no residual damage, and it is adjustable with the use of a programmable stimulator. Only DBS is funded through Medicare (see MBS items for DBS in Table 2) and as such, it is considered the primary comparator for the submission. DBS may be performed unilaterally or bilaterally; however as both procedures are performed at the same time many patients elect to undergo bilateral surgery due its superior clinical effectiveness. The application form provided historical (5-year) utilisation of DBS in Table 3, estimating approximately 250 procedures performed annually, mostly bilateral.

Table 2 MBS items for Deep Brain Stimulation

MBS item number	MBS item descriptor	Fee
40850	DEEP BRAIN STIMULATION (unilateral) functional stereotactic procedure including computer assisted anatomical localisation, physiological localisation including twist drill, burr hole craniotomy or craniectomy and insertion of electrodes	\$2,300.70
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	\$4,026.40
40852	DEEP BRAIN STIMULATION (unilateral) subcutaneous placement of neurostimulator receiver or pulse generator	\$346.05
40854	DEEP BRAIN STIMULATION (unilateral) revision or removal of brain electrode	\$534.80
40856	DEEP BRAIN STIMULATION (unilateral) removal or replacement of neurostimulator receiver or pulse generator	\$259.55
40858	DEEP BRAIN STIMULATION (unilateral) placement, removal or replacement of extension lead	\$534.80
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	\$2,055.05
40862	DEEP BRAIN STIMULATION (unilateral) electronic analysis and programming of neurostimulator pulse generator	\$163.85

Source: p29 of Application Form

Note: All above MBS item codes are indicated for "Essential tremor or dystonia where the patient's symptoms cause severe disability".

Table 3 Utilisation of MBS items for DBS

MBS item	Description	2014	2015	2016	2017	2018
40850	Unilateral DBS	16	12	10	16	19
40851	Bilateral DBS	217	245	235	233	226
-	Total DBS	233	257	245	249	245

Source: Table 4, p32 of application form

PASC confirmed that the main comparator is deep brain stimulation (DBS), unilateral or bilateral, noting that DBS is used to treat a broader range of conditions including Parkinsonian tremor, ET and dystonia. PASC noted that DBS has the advantage of being reversible, and appears to have a different safety profile compared with MRgFUS.

The applicant agreed that the main comparator is DBS, unilateral or bilateral. While DBS is used for a broader range of conditions, the applicant noted only data relevant to ET will be used in the ADAR.

It is, however, acknowledged that there may be a group of medically refractory ET patients who are currently receiving BSC because they are unwilling to accept the risks associated with DBS or are contraindicated for the procedure. This may include continued optimised medical therapy, as

described above, despite its limited efficacy where no alternative options are available. MRgFUS offers these patients a treatment option that does not require burr-hole craniotomy, craniectomy or general anaesthesia. As such, BSC may be a potential secondary comparator in a subgroup of the proposed population.

As per the clinical algorithm shown in Figure 2, the positioning of MRgFUS will be in line with DBS and BSC. The application form indicated that MRgFUS will replace DBS, but will be used in addition to BSC. That is, for use in patients shown to be refractory or intolerant to medical therapy, and whose symptoms cause severe disability.

PASC noted DBS might be given in addition to best supportive care (BSC), which might include continued optimised medical therapy (i.e. medically refractory). PASC noted BSC alone would be a potential secondary comparator, given in a subgroup of the proposed population contraindicated or not suitable for surgery.

OUTCOMES

PASC noted that outcomes in the Draft PICO were aligned with outcomes chosen from a pivotal RCT, which was funded by the applicant (and others). PASC considered that objective and validated outcomes typically used for health technology assessment purposes should be chosen, rather than aligning the outcomes from a single trial. For example, health-related quality of life outcomes ideally should be reported with a standardised tool (e.g. 36-Item Short Form Survey [SF-36]) and disease specific tool (e.g. Quality of Life in Essential Tremor Questionnaire [QUEST]). Importantly, PASC considered it was unclear what the minimum clinically important difference (MCID) was for the Clinical Rating Scale for Tremor (CRST), which would be critical to interpreting the comparative clinical benefit. The applicant agreed and stated it would investigate this further during the assessment phase. PASC also advised that long-term outcomes should be included when available.

PASC suggested the following outcomes:

Patient-relevant outcomes

- **Safety Outcomes:**
 - **Adverse Events:**
 - **Numbness, paraesthesiae, ataxia, dysarthria, dysphagia, in short and long term (>12 months)**
 - **Intraprocedural harms (due to helmet or other events) as noted in RCT and observational studies**
 - **Failed procedure rate (skull thickness, claustrophobia/anxiety, other)**
- **Efficacy/ Effectiveness including, but not limited to, patient-relevant outcomes:**
 - **Number of patients with benefit (number reaching MCID threshold of tremor scale (if validated))**
 - **Median (not mean) benefit in tremor, using MCID of Clinical Rating Scale for Tremor (CRST)**
 - **Duration of adequate benefit (using MCID)**
 - **Recurrence of tremor necessitating further treatment**
 - **Need for retreatment with DBS**
 - **Ability to cease medications**

Current and proposed clinical management algorithms

Current clinical management algorithm for identified population

PASC advised in the current algorithm, that BSC should be clearly defined, including reference to medical optimisation.

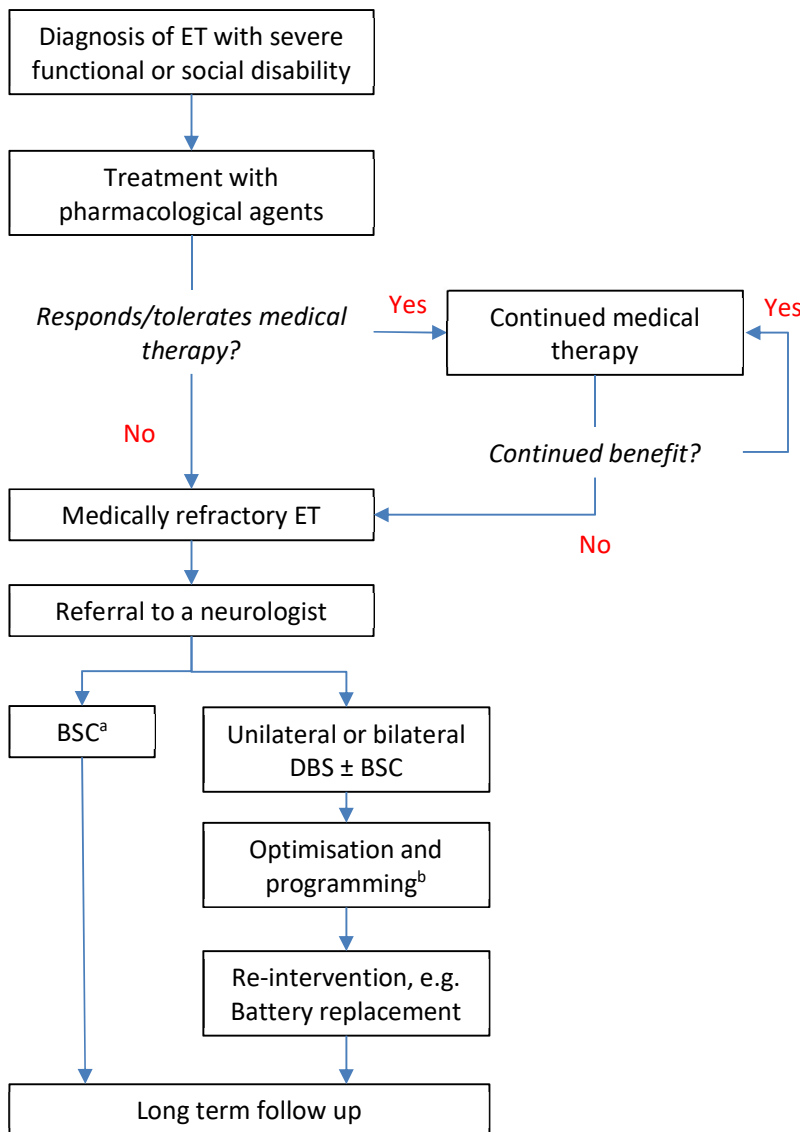


Figure 1. Current clinical management algorithm for ET

^a In those unwilling to accept the risks associated with DBS or are contra-indicated for the procedure

^b The Ontario HTA 2018 stated that according to the literature and clinical expert opinion tremor recurrence can nearly always be controlled by adjusting the stimulation level of the device (reprogramming) and therefore does not require reoperation

Proposed clinical management algorithm for identified population

PASC advised that in the proposed algorithm, there should be more detail in the MRgFUS clinical pathways, including stepping out the pre- and post-procedure imaging workup (specifically how many MRIs and the timing of these) and including relevant downstream outcomes and their associated management options.

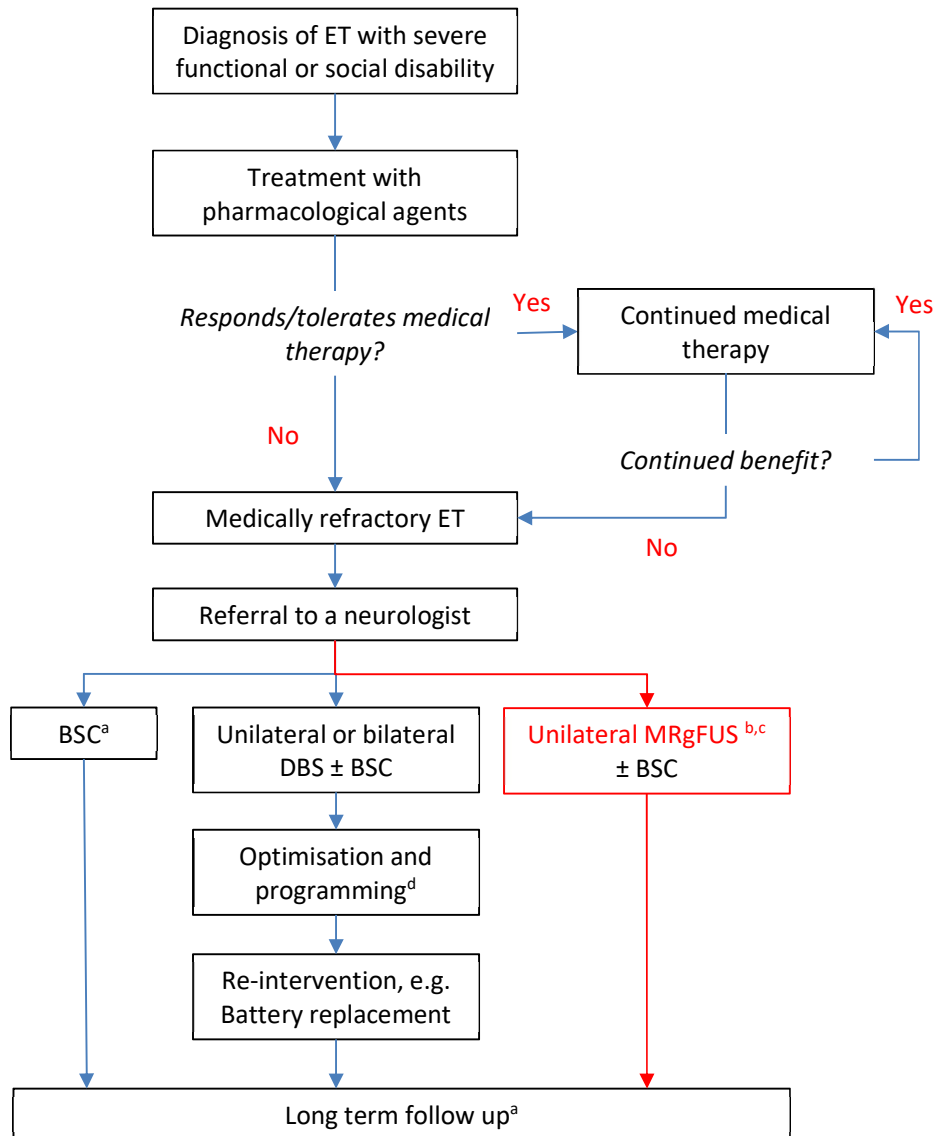


Figure 2. Proposed clinical management algorithm for ET

^a In those unwilling to accept the risks associated with DBS or are contra-indicated for the procedure

^b In Australian clinical practice currently, MRgFUS is provided as unilateral treatment. The application form stated that treatment of the contralateral side may be performed after a minimum of 6-12 months.

^c Following results from Elias et al. (2016), the Ontario HTA 2018 estimated 40% of people who undergo MRgFUS (or radiofrequency thalatomy) may undergo a second surgery once tremor recurs

^d The Ontario HTA 2018 stated that according to the literature and clinical expert opinion tremor recurrence can nearly always be controlled by adjusting the stimulation level of the device (reprogramming) and therefore does not require reoperation

The Applicant agreed with the PASC and confirmed that detailed descriptions of BSC and the proposed algorithm will be provided in the ADAR.

Proposed economic evaluation

The clinical claim is that MRgFUS in patients with medically refractory ET is non-inferior in safety and non-inferior in clinical effectiveness when compared with DBS, and that MRgFUS is inferior in safety and superior in clinical effectiveness when compared with BSC.

PASC confirmed that a cost-effectiveness analysis or cost-utility analysis is most appropriate. Although claiming non-inferiority, the technologies, side effects and outcomes appear different, so a cost-minimisation is not appropriate.

The Applicant agreed with the PASC.

It should be noted that the cost-effectiveness analysis should include also the price of the prostheses/devices and other consumable material needed for the delivery of DBS, as the material cost is far greater than the cost of the procedure itself (Appendix A, Table 4).

The applicant claims that DBS has already been established as cost-effective against BSC (MSAC Application 1109), and assuming MRgFUS is proven to be non-inferior to DBS and with lower costs, an economic evaluation of MRgFUS against BSC should not be required. It would automatically mean that MRgFUS would provide value for money relative to BSC.

Proposed MBS item descriptor and MBS fee

MBS item descriptors for radiology, neurology and neurosurgery components of the service are presented below. It was considered that the justification of the proposed items and fees will be important in the assessment report.

Patient preparation and pre-surgical planning

Before treatment, a specialised CT scan is performed to detail the shape, thickness and density of the patient's skull. The skull density ratio is calculated by the radiologist to assess whether sufficient energy can be delivered during the MRgFUS procedure and confirm patient suitability. A pre-operative MRI scan is also performed to exclude contraindications, assess the patient's anatomy and plan the treatment. The pre-operative MRI scan is fused with the CT to more accurately guide treatment. Patients with suitable imaging evaluations are progressed towards planning for the procedure. It was noted 5/81 patients from the pivotal RCT were excluded following randomisation but before their procedures due to: unsuitable skull (identified by skull density ratio from CT; n=2); patient withdrawal due to anxiety; vascular risk identified on MRI (missed on first interpretation) and investigator discretion.

The proposed MBS item wording and MBS fee for the pre-operative MRI scan of the brain (to assess suitability for MRgFUS) is based on other MBS 'MRI Scan of the Head' services.

Category 5 – DIAGNOSTIC IMAGING SERVICES

MAGNETIC RESONANCE IMAGING (including Magnetic Resonance Angiography if performed), performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by a specialist or by a consultant physician - scan of head for:

- assessment of suitability for treatment of essential tremor with MRI guided focussed ultrasound

Essential tremor where:

- (a) Symptoms cause severe disability, and
- (b) Tremor has proven refractory to, or recurred following, maximal medical therapy

Bulk bill incentive

(Anaes.)

MBS Fee: \$403.20 Benefit: 75% = \$302.40 85% = \$342.75

Planning and target verification

On the day of treatment, new images are acquired, with the patient positioned with the stereotactic frame and MRgFUS system in situ (utilising body coil). These images are co-registered with the pre-operative imaging data.

The proposed MBS item wording and MBS fee for MRI of the brain (and associated planning reports) is based on an existing MBS item for planning of stereotactic neurosurgery (MBS item 63010). The applicant notes that a new MBS item for this service may not be required.

Category 5 – DIAGNOSTIC IMAGING SERVICES

MAGNETIC RESONANCE IMAGING (including Magnetic Resonance Angiography if performed), performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by a specialist or by a consultant physician - scan of head for:

- stereotactic scan of brain, with Fiducials in place, for the sole purpose to allow planning for MRI guided focussed ultrasound

Bulk bill incentive

(Anaes.)

MBS Fee: \$336.00 Benefit: 75% = \$252.00 85% = \$285.60

Treatment/intraoperative procedure

Three items for unilateral MRgFUS are proposed for the intraoperative procedure: one for the neurosurgery, neurology, and radiology services provided, respectively. The applicant has advised against placing restrictions on the speciality of physicians performing these services, provided they are adequately trained and qualified. The applicant noted it is feasible the tasks may be performed by a physician from any of the three disciplines mentioned.

The application form stated that the proposed service would be delivered once per patient on the dominant side. The application form also stated that should the patient experience a recurrence of tremor, and the patient was assessed suitable by the treating physician for retreatment, then

MRI GUIDED FOCUSSED ULTRASOUND (unilateral), target localisation incorporating anatomical and physiological techniques, including intra-operative MRI imaging

Multiple Operation Rule

(Anaes.) (Assist.)

Claimable only once per patient per lifetime.

MBS Fee: To be determined Benefit: 75% = to be determined

PASC noted that the proposed item descriptor for intraoperative procedure with MRgFUS should be restricted to patients who do not have Parkinson's disease, noting that it is sometimes difficult to tell whether a patient has Parkinson's disease or ET. This has not been included in the MBS item descriptors above, given the difficulty in determining whether a patient has Parkinson's disease or ET. How to include this appropriately within the item descriptor, should be explored during the assessment phase.

The Applicant accepted that MRgFUS should be restricted to patients without PD. However, as previously stated, the applicant considered that ET Plus patients, where the dominant diagnosis is one of ET where additional neurologic signs such as dystonia, ataxia, and parkinsonism, are present should be eligible for treatment.

PASC noted retreatment was stated in the application to be permitted once only per patient, per side, but not included in the current item descriptor. The Applicant advised that retreatment was so uncommon that it would not impact the item descriptor. PASC also noted contralateral treatment was not relevant to this application as it was currently used for investigational purposes. Therefore, PASC considered as there is currently no evidence to support retreatment, the item descriptor should include a note stating that unilateral, once-only treatment is permitted. This has been updated in the item descriptors above.

The Applicant disagreed with the PASC and considered that inclusion of the contralateral treatment in the item descriptor is reasonable (see 'Population').

Confirmation whether the multiple operation rule applies, and whether this applies if different providers are billing for different parts of the procedure, will be undertaken.

Treatment outcome assessment

Treatment outcome is confirmed using post-treatment MRI scans at various intervals. The application form specified patients would undergo a MRI at three and/or six months follow-up; however, they have not proposed any restrictions of frequency of use for the proposed item descriptor.

The proposed MBS item wording and fee for MRI of the brain (to assess patient outcomes and exclude potential complications) is based on other MBS 'MRI Scan of the Head' services.

PASC queried if an item descriptor was necessary for the post procedure MRI performed at 3 and/or 6 months.

Category 5 – DIAGNOSTIC IMAGING SERVICES

MAGNETIC RESONANCE IMAGING (including Magnetic Resonance Angiography if performed), performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by a specialist or by a consultant physician - scan of head for:

- assessment of treatment outcomes following MRI guided focussed ultrasound procedure

Bulk bill incentive

(Anaes.)

MBS Fee: \$403.20 Benefit: 75% = \$302.40 85% = \$342.75

Consultation feedback

PASC noted that support was received from the Neurosurgical Society of Australia and the Royal Australian New Zealand College of Radiologists. PASC also noted the Royal Australian and New Zealand College of Radiologists (RANZCR) requested that interventional radiologists should be eligible to provide the service.

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 an ADAR (applicant-developed assessment report).

The applicant confirmed it intends to submit the ADAR in October 2020.

Appendix A

Table 4 Approximate cost profile for MRgFUS and comparison with DBS procedure

Cost item	MRgFUS		DBSa	
Resource Item	Cost	Reference	Cost	Reference
Neurosurgeon	\$2301-\$4026	Based on MBS items numbers 40850 and 40851	\$2301-\$4026	MBS items numbers 40850 and 40851
Neurologist MBS fee	\$2,055	Based on MBS items numbers 40860	\$2,055	MBS items number 40860
Radiologist fees	approx \$2000 to \$3000	Based on MBS item numbers for MRI Scan of the Head (5 to 6 in total before, during and after the procedure; see below)	Not applicable	\$0
Prostheses / Single use consumables	Price / Fee to be determined	Disposable patient kit See Question 12 of application form	Generator: \$8598, \$14307, \$18193, \$20,900 Leads: \$1995, \$3943, \$4337 External programmer: \$1330, \$1876 Electrodes \$1425 Accessories: \$166, \$190, \$523 Total: approx \$30,000 to \$40,000 depending on brand and quantity of various devices used	PL number: 040401 PL number: 040403 PL number: 040402 PL number: 040404 PL number: 040405
Anaesthesia	Variable depending on individual patient needs, but is generally very rare/minor given the patient needs to be conscious during the procedure	To be investigated in the ADAR	Variable depending on individual patient needs	To be investigated in the ADAR
Hospital admission	To be determined	Costs to incorporate: operating theatre amortisation of capital equipment ALOS of 1 to 2 days	\$22,255 to \$64,776 (depending on complexity/complications)	AR-DRGs B02A to B02C (as used in MSAC application 1109) ALOS of 6 to 19 days

Source: Table 5, p35 of application form

Note: This comparison of the cost profile is intended to compare the cost of the respective procedures themselves. It does not include costs associated with maintaining and/or replacing the DBS system and components over the lifetime of the patient. These costs will be investigated in full in the economic evaluation to be included in the ADAR.

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