



Australian Government
Medical Services Advisory Committee

Public Summary Document

Application No. 1614 – Magnetic resonance-guided focused ultrasound for the treatment of medically refractory essential tremor

Applicant: Insightec Ltd

Date of MSAC consideration: MSAC 81st Meeting, 31 March – 1 April 2021

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

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of magnetic resonance-guided focused ultrasound (MRgFUS) for medically refractory essential tremor (ET) was received from Insightec by the Department of Health.

2. MSAC’s advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and+ cost-effectiveness, MSAC did not support the creation of a new Medicare Benefits Schedule (MBS) item for magnetic resonance imaging-guided focused ultrasound in the treatment of medically refractory essential tremor. MSAC accepted that there was an unmet clinical need for a non-invasive intervention compared with MBS-funded deep brain stimulation, but considered that the comparative safety was too uncertain and – as a consequence – the economic evaluation was inappropriate. MSAC also noted issues with the procedural requirements, fee structure and frequency of imaging, and that the role of ipsilateral retreatment and contralateral (non-dominant) treatment was not supported by the current evidence base.

| Consumer summary |
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| <p>This application is from Insightec Ltd and seeks to create a new Medicare Benefits Schedule (MBS) item for magnetic resonance-guided focused ultrasound (MRgFUS). It would be used to treat medically refractory essential tremor.</p> <p>Essential tremor is a condition that causes uncontrolled shaking, mostly in the hands. This application is about refractory essential tremor, which means that the condition does not respond to treatment.</p> <p>Deep brain stimulation (DBS) is often used to control the symptoms of refractory essential tremor. However, this is an invasive procedure that involves drilling holes into the skull</p> |

Consumer summary

and putting an electrode deep in the brain. MRgFUS uses focused ultrasound waves that penetrate the skull and make changes to the brain tissue which is the cause of the abnormal movements, without the need to make an incision or drill holes in the skull to achieve a similar result.

MSAC accepted that there will be patients who would prefer to use MRgFUS rather than the more invasive procedure of DBS to manage refractory essential tremor. However, MSAC noted that the level of evidence is very poor for MRgFUS, which means that MSAC was unable to ensure that MRgFUS is at least as safe, clinically effective and cost effective as DBS. For these reasons, MSAC did not support this proposed listing.

MSAC's advice to the Commonwealth Minister for Health

MSAC did not support the creation of a new MBS item for magnetic resonance imaging-guided focused ultrasound in the treatment of medically refractory essential tremor. MSAC accepted that there are some people who need a non-invasive intervention compared with MBS-funded deep brain stimulation. However, MSAC considered that due to the different safety profiles of the technologies the comparative safety was too uncertain, which meant that the economic evaluation, which did not take into account differences in benefits and harms, was not appropriate.

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

MSAC noted that this application from Insightec Ltd seeks to create a new MBS item for MRgFUS for the treatment of medically refractory essential tremor (ET).

MSAC noted the supportive consumer feedback for this application from a charity group (Parkinson's South Australia and Northern Territory). MSAC also noted the consumer issues raised at ESC for the proposed intervention.

MSAC considered that there was an unmet clinical need for a non-invasive intervention such as MRgFUS, compared with invasive deep brain stimulation (DBS). MSAC also noted that MRgFUS creates an irreversible thalamic lesion, unlike DBS which is reversible.

MSAC noted the applicant-developed assessment report (ADAR) included tremor recurrence to allow for retreatment in the algorithm.

MSAC noted that the clinical claim is that MRgFUS is:

- non-inferior with respect to clinical efficacy and with a different yet non-inferior safety profile compared with DBS as the main comparator
- superior with respect to clinical efficacy and inferior with respect to safety, compared with best standard care (BSC) as the potential secondary comparator.

MSAC considered the evidence for MRgFUS *vs.* DBS, noting it included two retrospective studies, one systematic review and indirect treatment comparison, and a naïve comparison of single-arm studies (mainly case series) of MRgFUS (n = 9) and DBS (n = 2), with no direct head-to-head randomised controlled studies (RCTs). For MRgFUS *vs.* BSC, MSAC noted the pivotal evidence was an RCT comparing MRgFUS with a sham procedure over a 3-month follow-up period. MSAC noted the evidence was supplemented with three follow up reports

of the intervention arm of the RCT over four years. Overall, MSAC considered the existing evidence base was at a high risk of bias.

Regarding comparative safety of MRgFUS *vs.* DBS, MSAC noted that meaningful comparison is difficult due to the two procedures having a different safety profile:

- Intra-procedural adverse events (AEs) were common with MRgFUS *vs.* no intra-procedural sensations with DBS as inserted under general anaesthesia
- No serious AEs for MRgFUS *vs.* serious AEs from potential hardware-related complications with DBS
- Post procedural AEs including paraesthesia and gait disturbances were either transient or improve with time *vs.* AEs including balance or gait difficulties and speech disturbance, with some resolving after hardware programming with DBS.

MSAC considered that the claim that AEs are only short term with MRgFUS is uncertain. Overall, MSAC agreed with ESC and considered that there is an uncertain safety profile.

Regarding comparative effectiveness of MRgFUS *vs.* DBS, MSAC noted that no minimum clinically important difference (MCID) had been established for any of the tremor scales, despite PASC considering this to be critical to include. Although statistically significant differences before and after treatment were found in several studies, whether the differences were also clinically significant remains unknown. In addition, MSAC noted the ESC advice for comparative effectiveness but considered that it could not be confident in the magnitude of treatment effect due to the limited and low-quality comparative evidence, small numbers of patients, different methods of assessment of tremor severity, limited long-term follow-up of MRgFUS (indirect treatment comparison was limited to 12 months), and in particular no MCID has been established and validated for ET.

Regarding retreatment, MSAC noted the applicant acknowledges that there is currently insufficient evidence to support retreatment, that that treatment of the contralateral (non-dominant) side is currently investigational and that there is currently no data on contralateral treatment, although trials are underway. MSAC considered that the role of repeat and contralateral MRgFUS is contentious and that more data are needed.

Overall and based on the available data, MSAC considered that the claim of comparative effectiveness was uncertain.

MSAC noted that due to the different safety profiles, the appropriate economic analysis for the evaluation, as advised by PASC, should have been a cost-effectiveness analysis (CEA) or cost-utility analysis (CUA). However, the ADAR presented a cost-minimisation assessment. MSAC considered a CUA could have been done, noting ESC identified a cost-utility analysis that was done by Ontario Health Technology Assessment in 2018 that showed that the incremental cost-effectiveness ratio (ICER) of DBS compared with MRgFUS neurosurgery is \$134,259 per quality-adjusted life year (QALY) gained.

MSAC noted several issues with the proposed item descriptors:

- The ADAR did not make a strong case to justify the high fees that were proposed, particularly the proposed MBS fee for presurgical planning, which was increased compared to that in the ratified PICO
- The need for involvement of all three specialist personnel (neurologist, neurosurgeon and neuroradiologist, and the associated item numbers and costs) should be better

justified. If all are required, the specific roles and thus time commitments of each needs to be clarified.

- The need for separate MRI scans for suitability and planning should be better justified, as well as the need for a special post-treatment MRI item.

MSAC agreed with ESC and considered that the item descriptor should be restricted to unilateral, once-only treatment. MSAC noted the pre-MSAC response that the applicant is willing to work with the Department to develop a restriction for MRgFUS that is both clinically acceptable and consistent with the evidence.

MSAC considered whether it would be possible limit this population to those who are considering using MRgFUS as an alternative to DBS. However, it was noted that this would be a difficult population to adequately define.

MSAC noted that a better understanding of projected case load is needed, as there could be a large demand for this treatment from people who would prefer to not undergo DBS given a choice. MSAC agreed with ESC that the ADAR likely underestimated the budget impact, with remaining uncertainty of whether the MBS funding of MRgFUS will “grow the market”.

MSAC also noted that the availability of the proposed intervention in the future needs to be addressed for equity of access, as currently the procedure is only available in one centre in Australia. MSAC considered that it may be useful to consult with the relevant societies on how the equity issue could be addressed.

MSAC considered that any resubmission would need to carefully define the eligible population, as there may be a high clinical need in a particular subgroup of patients currently treated with DBS that MRgFUS could be restricted to. In addition, MSAC considered that the economic evaluation comparing MRgFUS vs. DBS should be a CEA or CUA due to the uncertainty regarding comparative safety, and that when more clinical evidence is available it should be included in any future application, including for retreatment and contralateral treatment (if available). MSAC also suggested that a resubmission should have a packaged item rather than the six separate items within one application.

4. Background

This is the first submission for magnetic resonance-guided focused ultrasound (MRgFUS) in patients with medically refractory ET. MSAC has not previously considered this application.

The ADAR stated that the applicant intends to lodge an application to the Prostheses List Advisory Committee's (PLAC) for the kit to be considered for the Prostheses List (PL). The pre-MSAC response confirmed the applicant had submitted an application to include the ExAblate Neuro Patient Accessory Kit on part C of the PL (reference number of N002552).

5. Prerequisites to implementation of any funding advice

Items on the Australian Register of Therapeutic Goods (ARTG) relevant to this application are shown in Table 1. The two ARTG listings are identical with alternative distributors (GE and Medigroup). The intended purpose on the ARTG is described as follows: “to produce and control the delivery of high heat, i.e. temperatures greater than 43 degrees Celsius, to the body for the treatment of malignant or benign tumours, or other disease conditions”.

Table 1 MRgFUS systems listed on the ARTG

| ARTG no. | Product no. | Product description | Product category | Sponsor | Manufacturer |
|----------|-------------|---------------------------------|--------------------------|---------------------------------|---------------|
| 260438 | 40781 | Hyperthermia system, ultrasound | Medical Device Class IIb | Medigroup Pty Ltd | InSightec Ltd |
| 128137 | 40781 | Hyperthermia system, ultrasound | Medical Device Class IIb | GE Healthcare Australia Pty Ltd | InSightec Ltd |

Source: Table 7, p35 of the ADAR

In the pre-MSAC response, the applicant noted that the ARTG listing 260438 has been transferred to Getz Healthcare (from Medigroup Pty Ltd).

6. Summary of public consultation feedback/consumer issues

Support was received for the application from one charity group (Parkinson’s South Australia and Northern Territory) and two societies: the Neurosurgical Society of Australasia (NSA) and the Royal Australian New Zealand College of Radiologists (RANZCR).

RANZCR requested that interventional radiologists should be eligible to provide the service. The NSA addressed two patient safety concerns in their letter of support for the application. The NSA considered it would be inappropriate for the proposed service to be offered by isolated practitioners and recommended that it should be managed by multidisciplinary teams. In addition, the NSA was also concerned with specific wording regarding who will primarily deliver the proposed service; it was recommended that a neurosurgeon should be specified as the primary proceduralist, supported by a movement disorder neurologist and neuroradiologist.

The Consumer Evidence and Engagement Unit (CEEU) within the Office of Health Technology Assessment of the Department presented information to PASC regarding consumer comments that were submitted as part of a NICE consultation on a similar consideration. The CEEU noted that although the comments may not be applicable to the proposed population in this application, the comments could be helpful in identifying outcomes that are important to patients.

One targeted consultation survey was also received from a specialist. The specialist considered some advantages to the proposed service would be the ability to get real time feedback and the ability to retreat, as well as the service being an alternative for patients unfit for surgery. One disadvantage may be considered that the patient is required to have their full head shaved.

There was no other public consultation feedback received for this application from consumers.

7. Proposal for public funding

The ADARs proposed MBS item descriptors for MRgFUS include several components: pre-surgical suitability assessment with MRI (Table 2), pre-surgical planning with MRI (Table 3), treatment/intraoperative delivery of neurology services of MRgFUS (Table 4), treatment/intraoperative delivery of neurosurgical services of MRgFUS (Table 5), treatment/intraoperative delivery of radiology services of MRgFUS (Table 6) and post-surgical assessment with MRI (Table 7).

Table 2 Proposed MBS item descriptor – pre-surgical suitability assessment

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| Category 5 –DIAGNOSTIC IMAGING SERVICES |
| <p>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:</p> <ul style="list-style-type: none"> - assessment of suitability for treatment of essential tremor with MRI-guided focused ultrasound <p>Essential tremor where:</p> <ul style="list-style-type: none"> (a) Symptoms cause severe disability, and (b) Tremor has proven refractory to, or recurred following, maximal medical therapy <p>The service is not applicable to patients with a primary diagnosis of Parkinson's disease^a</p> <p>Bulk bill incentive (Anaes.)</p> |
| Fee: \$403.20 Benefit: 75% = \$302.40 85% = \$342.75 |

Source: Table 8, pp 38-39 of the ADAR

^aNote: Does not exclude patients with a primary diagnosis of ET with parkinsonian features consistent with the definition of ET plus

Table 3 Proposed MBS item descriptor – pre-surgical planning

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| Category 5 –DIAGNOSTIC IMAGING SERVICES |
| <p>MAGNETIC RESONANCE IMAGING (including Magnetic Resonance Angiography if performed) and stereotactic anatomic localisation, 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:</p> <ul style="list-style-type: none"> - stereotactic scan of brain, with frame in place - Computerised planning and target verification <p>For the sole purpose of conducting MRI-guided focused ultrasound</p> <p>Bulk bill incentive (Anaes.)</p> |
| Fee: \$994.60 Benefit: 75% = \$745.95 85% = \$845.41 |

Source: Table 8, pp 38-39 of the ADAR

Note: The item proposed in the ADAR lists a "stereotactic scan of brain, with frame in place; computerised planning and target verification", instead of "stereotactic scan of brain, with fiducials in place" (item 63010 [fee: \$336] and Ratified PICO proposal). In addition, the proposed fee of \$994.60 is higher than the Ratified PICO based on MBS item 63010 (fee: \$336)

Table 4 Proposed MBS item descriptor – treatment/intraoperative procedure (neurology services)

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| Category 5 –DIAGNOSTIC IMAGING SERVICES |
| <p>MRI-GUIDED FOCUSED ULTRASOUND (unilateral), target localisation incorporating anatomical and physiological techniques, including intraoperative clinical evaluation</p> <p>Multiple Operation Rule (Anaes.) (Assist.)</p> |
| Fee: \$2,055.05 Benefit: 75% = \$1,541.29 |

Source: Table 8, pp 38-39 of the ADAR

Table 5 Proposed MBS item descriptor – treatment/intraoperative procedure (neurosurgery services)

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| Category 3 – THERAPEUTIC PROCEDURES |
| MRI-GUIDED FOCUSED ULTRASOUND (unilateral) procedure including computer assisted anatomical localisation, physiological localisation, and lesion production in the basal ganglia, brain stem, thalamus or deep white matter tracts, for the treatment of: Essential tremor where: (a) Symptoms cause severe disability, and (b) Tremor has proven refractory to, or recurred following, maximal medical therapy The service is not applicable to patients with a primary diagnosis of Parkinson's disease ^a Multiple Operation Rule (Anaes.) (Assist.) |
| Fee: \$3,165.50 Benefit: 75% = \$2,372.62 |

Source: Table 8, pp 38-39 of the ADAR

^aNote: Does not exclude patients with a primary diagnosis of ET with parkinsonian features consistent with the definition of ET plus

Table 6 Proposed MBS item descriptor – treatment/intraoperative procedure (radiology services)

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| Category 3 – THERAPEUTIC PROCEDURES |
| MRI-GUIDED FOCUSED ULTRASOUND (unilateral), target localisation incorporating anatomical and physiological techniques, including intraoperative MRI imaging Multiple Operation Rule (Anaes.) (Assist.) |
| Fee: \$806.40 Benefit: 75% = \$604.80 85% = \$685.44 |

Source: Table 8, pp 38-39 of the ADAR

Table 7 Proposed MBS item descriptor – post-surgical treatment assessment

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| Category 3 – THERAPEUTIC PROCEDURES |
| 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 focused ultrasound procedure Bulk bill incentive (Anaes.) Claimable only once per patient per procedure |
| Fee: \$403.20 Benefit: 75% = \$302.40 85% = \$342.75 |

Source: Table 8, pp 38-39 of the ADAR

In the Ratified PICO, proposed MBS items for the treatment/intraoperative procedure (listed above in Table 4, Table 5 and Table 6) include a note that the item is “Claimable only once per patient per lifetime”. The applicant decided to remove this note from the proposed listing as they disagreed with the PASC, thus allowing re-treatment or contralateral treatment. In the pre-ESC response, the applicant consulted with a clinical expert advising that explicitly mandating against retreatment unnecessarily removes the autonomy of the treating physician, and provided the reasons why retreatment may be clinically appropriate.

The commentary noted that the item fee for pre-surgical planning as proposed in the ADAR (Table 3) is different from the fee proposed in the Ratified PICO (see Note to Table 3; proposed fee \$994.60 vs. \$336.00). There is also a difference in the descriptor wording of the

MBS item proposed in the ADAR compared to the Ratified PICO. The item proposed in the ADAR lists a “stereotactic scan of brain, with frame in place; computerised planning and target verification”, instead of “stereotactic scan of brain, with fiducials in place” (item 63010 and Ratified PICO proposal).

In the pre-ESC response, the applicant indicated that the discrepancy is a result of a misunderstanding of the requirements for each stage of the procedure in the PICO. It was mistakenly understood that the first MRI was the planning stage which was later found to be an assessment of suitability for MRgFUS. The second imaging stage was initially thought to be a “stereotactic scan of brain, with fiducials in place” (as per the PICO) however, following further communication with clinical experts, it was understood that this service also requires a computerised planning component which requires greater time. The increase in cost reflects this greater planning time.

The additional cost of \$658 for the planning component of this service was based on MBS item 40800 which was discontinued shortly after the ADAR was lodged. Nevertheless, the fee for the 40800 item number was only used as a benchmark for the expertise and intensity of the service required for the purposes of estimating a reasonable MBS fee.

8. Proposed intervention’s place in clinical management

Description of Proposed Intervention

MRgFUS is a method of targeted tissue thermal ablation used to treat medically refractory ET. The ablation target is the ventral intermediate nucleus (Vim) of the thalamus. Magnetic resonance imaging (MRI) provides detailed images of the brain in real time during the surgery and permits precise localisation and real-time monitoring of the targeted tissue to prevent collateral damage to surrounding healthy tissue. A high-intensity focused ultrasound transducer allows for ultrasound beam steering and focusing without attenuation. Ultrasound waves interact with biological tissue and produce a variety of effects including acoustic cavitation, shear stress, and thermal effect through a vibration of molecules, which in turn generate frictional heat. Protein denaturation or coagulative necrosis occur in the cells. The delivery of the thermal ablation is done through an intact skull, without the need for incision or craniotomy.

Description of Medical Condition(s)

The proposed population for treatment with MRgFUS are adults with medically refractory ET and symptoms causing severe disability. Patients are required to be under the care of a neurologist, with disability defined as either functional or social. MRgFUS is proposed only for patients where the primary cause of tremor is ET, i.e. excluding Parkinson’s disease and dystonia. It is proposed that medically refractory be defined as failure 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). The Commentary noted that the definition of “adequate benefit” has neither been defined in the ADAR nor the Ratified PICO and PASC has previously queried whether ‘medically refractory’ should be defined in the proposed population and what duration is required before a patient is considered medically failed ([1614 Ratified PICO Confirmation](#), p5).

Clinical Place

The clinical management algorithm for patients with ET that depicts the intended use and positioning of MRgFUS following a listing on the MBS is provided in Figure 1. MRgFUS is carried out as an in-patient procedure and requires an overnight hospitalisation. The ADAR noted that MRgFUS is positioned in line with DBS and BSC, offering a treatment alternative to patients unwilling to accept the risks associated with DBS or are contraindicated for the procedure, as per the nominated comparators. Patients experiencing tremor recurrence following MRgFUS or DBS may seek further treatment depending on the severity of the tremor. These patients may undergo a (further) MRgFUS procedure, elect to undergo DBS or remain on BSC.

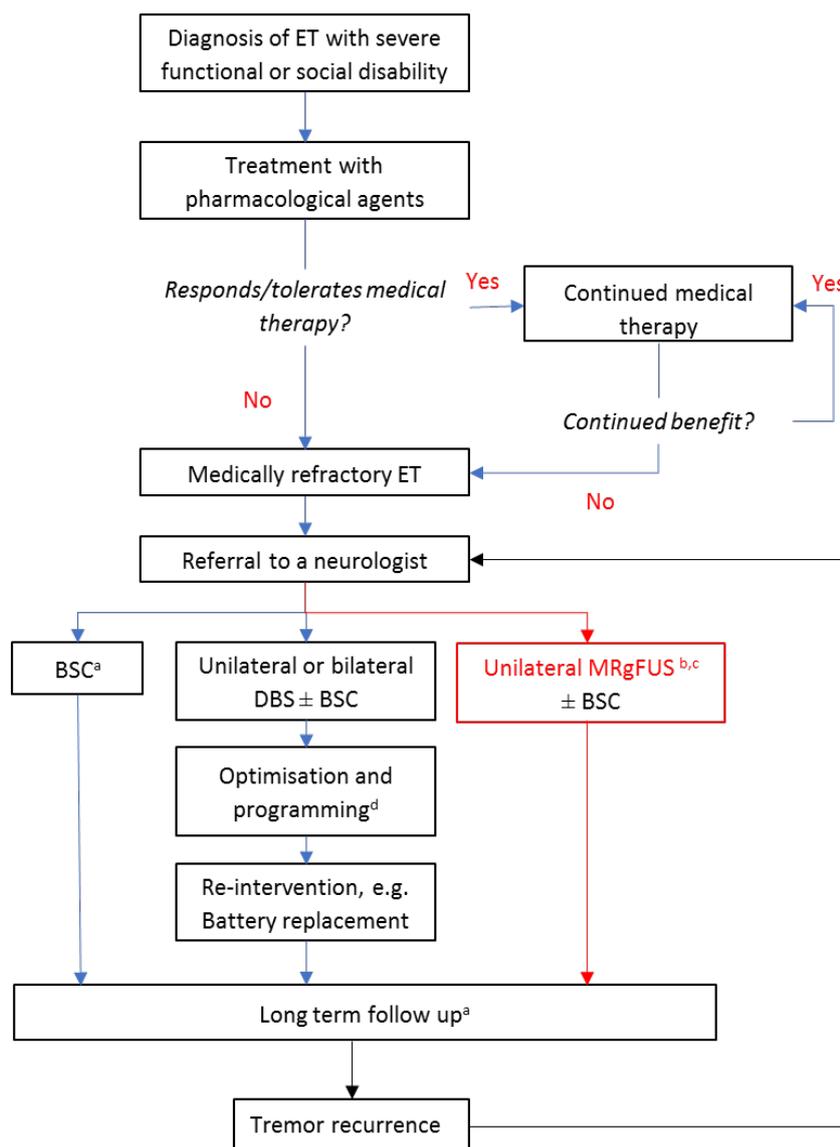


Figure 1 Clinical management algorithm for MRgFUS relative to current clinical practice (proposed service in red)

Source: Figure 3, p 48 of the ADAR

Abbreviations: BSC, best supportive care; DBS, deep brain stimulation; ET, Essential tremor; MRgFUS, magnetic resonance-guided focused ultrasound

^a In those unwilling to accept the risks associated with DBS or are contraindicated 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 See Figure 2 for further detail on the pre- and post-procedure imaging workup required in the MRgFUS clinical pathway

^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

To provide further detail in the MRgFUS clinical pathway, the ADAR provided a supplementary algorithm to detail the pre- and post-procedure imaging workup required, at PASC's request (Figure 2).

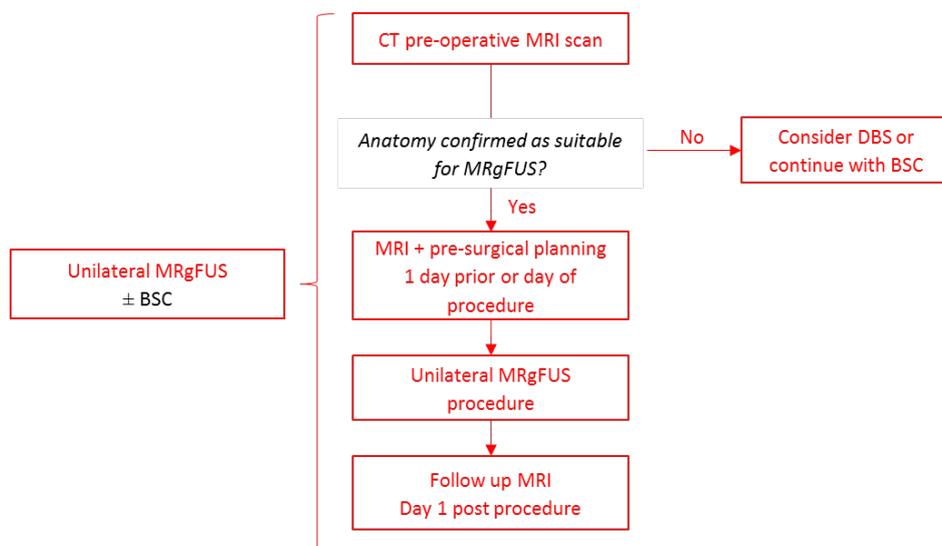


Figure 2 MRgFUS clinical pathway

Source: Figure 4, p 49 of the ADAR

Abbreviations: BSC, best supportive care; CT, computerised tomography; MRgFUS, magnetic resonance-guided focused ultrasound; MRI magnetic resonance imaging

Note: The procedure itself requires a number of brief MRIs to be conducted throughout (average 3 or 4 hours) with and a further standard MRI immediately following the procedure (of 45 minutes duration with formal report).

9. Comparator

Unilateral or bilateral DBS is proposed as the main comparator for MRgFUS. DBS involves inserting a permanent electrode via a burr hole in the skull into the thalamus, or other region of the brain causing the tremor. This electrode is then connected via a wire to a pacemaker box located in the chest region to enable electrical stimulation of the VIM Zaaroor et al., 2017¹. DBS is performed during hospital admission, with MBS-listed procedures performed under general anaesthesia (MBS items 40850, 40851, 40852, 40854, 40856, 40858, 40860, 40862; Table 21). The ADAR stated that the intervention requires at least one night of observation in the intensive care unit and a minimum of one week thereafter at the neurosurgical ward.

Best supportive care (BSC) is proposed as the second comparator, despite its limited efficacy where no alternative options are available.

10. Comparative safety

The ADARs evidence base to inform the relative efficacy and safety of MRgFUS and DBS (Comparison 1) comprised of:

- two retrospective comparative studies (Level III evidence),
 - Huss et al. (2015)² compared the safety and clinical effectiveness of MRgFUS vs. unilateral and bilateral DBS by way of a retrospective

¹ Zaaroor M, Sinai A, Goldsher D, Eran A, Nassar M, Schlesinger I. Magnetic resonance-guided focused ultrasound thalamotomy for tremor: a report of 30 Parkinson's disease and essential tremor cases. *J Neurosurg.* 2018 Jan;128(1):202-210. doi: 10.3171/20

² Huss, D. S., et al. (2015). "Functional assessment and quality of life in essential tremor with bilateral or unilateral DBS and focused ultrasound thalamotomy." *Movement Disorders* 30(14): 1937-1943.

- longitudinal database analysis, using the Clinical Rating Scale of Tremor (CRST) scale for tremor measurement
- Kim et al. (2017)³ retrospectively compared MRgFUS and unilateral DBS, using a non-validated patient response scale.
- a systematic review and indirect treatment comparison (ITC) by Langford et al. 2018⁴ (Level III evidence), and
- a naïve comparison conducted with two non-comparative DBS studies and nine non-comparative (mainly case series) MRgFUS studies (Level IV evidence).

Of the two non-comparative DBS studies, the ADAR considered that one was considered to have a low risk of bias and one was considered to have a moderate risk of bias. While the non-comparative MRgFUS studies were conducted in the USA, Europe, Korea and Japan, the DBS studies included in the ITC and naïve comparison were largely limited to the USA suggesting that there may be some exchangeability issues. The commentary considered that overall, the available evidence was found to be at a high risk of bias.

A total of ten studies were considered relevant to the evidence base for MRgFUS vs. BSC. The pivotal evidence is a sham-controlled multicentre randomised controlled trial (RCT) by Elias et al. 2016⁵ (Level II evidence) considered by the ADAR to have a low risk of bias. However, the commentary considered the RCT assessed to be at severe risk of bias. Nine prospectively conducted non-comparative MRgFUS studies were included as supportive evidence to demonstrate consistency and durability of effect.

Adverse events

MRgFUS vs. DBS

The ADAR stated that the comparative study reported by Huss 2015 demonstrated intraprocedural adverse events (AEs) to be common during the MRgFUS procedure. All were mild or moderate, transient and resolved. No intraprocedural adverse events were reported in the DBS groups.

The ADAR noted that the most common post-procedure AEs reported for MRgFUS were paraesthesia (93.3%) and gait instability (33.3%), the majority of which were transient and resolved by 12 months. Gait instability (84.6%) was frequently observed in patients undergoing unilateral DBS while gait instability and dysarthria were equally as common in bilateral DBS (17.5%). As observed in the MRgFUS group, the majority of DBS-related AEs resolved within the 12 months follow-up. Serious AEs related to DBS hardware placement comprising infection (1.7%), lead erosion (3.5%) and haemorrhage (3.5%) were reported in patients undergoing bilateral DBS only. The risk of infection and hardware complications was also reported in the large, controlled trial reported by Wharen et al. (2017)⁶ in which 13.4% of patients required re-intervention due to device malfunctions. These events have not been reported following MRgFUS reflecting the incisionless nature of the intervention and lack of implantable device required.

³ Kim, M., et al. (2017). "Comparative Evaluation of Magnetic Resonance-Guided Focused Ultrasound Surgery for Essential Tremor." *Stereotactic and Functional Neurosurgery* 95(4): 279-286.

⁴ Langford, B. E., et al. (2018). "Focused Ultrasound Thalamotomy and Other Interventions for Medication-Refractory Essential Tremor: An Indirect Comparison of Short-Term Impact on Health-Related Quality of Life." *Value in Health* 21(10): 1168-1175.

⁵ Elias, W. J., et al. (2016). "A randomized trial of focused ultrasound thalamotomy for essential tremor." *New England Journal of Medicine* 375(8): 730-739

⁶ Wharen, R. E., Jr., et al. (2017). "Thalamic DBS with a constant-current device in essential tremor: A controlled clinical trial." *Parkinsonism Relat Disord* 40: 18-26.

Overall, the ADAR assessed MRgFUS and DBS to have different short-term safety profiles. The adverse events observed for both treatments were generally mild or moderate in nature and transient, with the majority of complications resolving within 3 to 12 months. Consequently, there are no discernible differences in the long-term safety of these treatment supporting a claim of different yet non-inferior safety of MRgFUS relative to DBS. Given the risks of infection, haemorrhage and hardware complications associated with DBS, this claim is considered conservative.

MRgFUS vs. BSC

The ADAR noted a greater proportion of patients treated with MRgFUS experienced procedure-related AEs when compared to sham (N=50; 89% vs. N=12; 60%) as reported in the pivotal RCT.

The ADAR also noted that two patients receiving MRgFUS experienced serious adverse events. One patient had dense and permanent hypesthesia of the dominant thumb and index finger and one patient had a transient ischemic attack 6 weeks after the procedure which was not considered to be related to the study procedure. All remaining AEs observed in the MRgFUS were mild or moderate and resolved over the 12-month study period. Long-term efficacy reported in the open-label study at 3 and 4 years showed a further decline in AEs over time in both number and intensity with no new AEs reported. The safety profile observed in the non-comparative studies were consistent with the pivotal trial. AEs were mostly transient with no additional safety signals observed.

The ADAR considered that although MRgFUS has an inferior safety profile relative to BSC, the evidence demonstrates the procedure to be safe and well tolerated.

11. Comparative effectiveness

MRgFUS vs. DBS

The ADAR noted that the Huss 2015 study showed there was no significant differences between MRgFUS and unilateral/bilateral DBS with respect to reduction in hand tremor and tremor-related disability (Mean difference: 3.4% and 0.0%; 5.3% and 3.0%; for each outcome respectively). Similarly, no significant difference was observed between the MRgFUS and bilateral DBS groups in relation to quality of life (68.0% vs 72.0%; mean difference: 4.0%). The ADAR considered that the greater reduction in total tremor measured using the clinical rating scale for tremor (CRST) following bilateral DBS (23.8%; $p < 0.05$) compared to MRgFUS, likely reflects the inclusion of bilateral measures of tremor in the total CRST. Importantly, the ADAR noted that tremor-related disability and quality of life were not significantly different between the treatment groups, which demonstrates that the majority of benefit observed from treatment of ET is derived from treating the dominant side and that limited functional gain is achieved from treating the contralateral side.

The ADAR noted that based on a responder analysis presented in the Kim (2017) study, the criterion for successful treatment defined as achieving 90-100% resolution of tremor was 16 patients (84.2%) in the DBS group, and 18 patients (78.3%) in the MRgFUS group with no significant differences detected between the two treatment modalities ($p = 0.62$). Complete remission was observed in 9 (47.4%) DBS patients, and 8 (34.8%) MRgFUS patients. The ADAR noted that the ITC was limited to the CRST Part C and the total CRST reported at 12 months. The ADAR also acknowledged that there are substantial limitations in the study, the results of the matching-adjusted indirect comparison (MAIC) and simulated treatment comparison (STC) analyses support the retrospective comparative study suggesting there to be no difference in the reduction of total tremor (MAIC: 0%; STC: 0.31% [95% confidence

interval (CI): -2.53 to 3.16]) and tremor-related disability (MAIC: 0%; STC: -4.35% [95% CI: -12.82 to 4.13]) between MRgFUS and DBS.

The ADAR also noted that little difference was observed between the two surgical approaches in the naïve comparison of non-comparative DBS and MRgFUS studies in relation to total CRST (56.5% vs. 55.1% for MRgFUS vs DBS; mean difference: 1.4%) or tremor-related disability (68.2% vs. 71.4% for MRgFUS vs DBS; mean difference: 3.2%).

A summary of findings is shown in Table 8. Collectively, the ADAR considered that these data support a clinical claim of non-inferior efficacy of MRgFUS relative to DBS.

The commentary noted that the existing evidence base for Comparison 1 (MRgFUS vs. DBS) was found to be at high risk of bias due to limited comparative evidence. The commentary considered that both MRgFUS and DBS, appear to be effective at significantly reducing tremor (total and hand tremor), tremor-related disability and improving quality of life, at least in short to medium term (up to four years of follow-up for MRgFUS). The commentary also considered that the evidence available does not allow to unequivocally conclude whether the clinical effectiveness of MRgFUS is significantly different from DBS. Both MRgFUS and DBS achieved statistically significant improvements from baseline to last follow-up in total tremor (CRST total, percentual change from baseline, range, 35.3-69.6% for MRgFUS and 32.8-79.5% for DBS), hand tremor (range, 43.4-78% for MRgFUS and 44.8-78.9% for DBS), tremor-related disability (Part C of the CRST, range, 55.1-85.4% for MRgFUS and 49.3-88.4% for DBS), and quality of life (QUEST-SI, range 37.1-67.6% for MRgFUS, not interpretable for DBS).

Table 8 Balance of clinical benefits and harms of MRgFUS, relative to DBS, and as measured by the critical patient-relevant outcomes in the key studies

| Outcomes (units) Follow-up | Participants (studies) | Quality of evidence (GRADE) | Reduction with MrgFUS | Reduction with DBS | Mean difference | Comments |
|-----------------------------------|----------------------------------|-----------------------------------|-----------------------------|----------------------------|--|---|
| Retrospective comparative studies | | | | | | |
| Total CRST, 12 months | MRgFUS=15; uDBS=13; bDBS=57; k=1 | ⊕⊕⊕⊖ | 55.7% | uDBS: 73.4% bDBS: 79.5% | MRgFUS vs uDBS: 17% MRgFUS vs bDBS: 23.8% | Numerically favours uDBS Statistically favours dDBS (p<0.05) |
| Hand tremor, 12 months | MRgFUS=15; uDBS=13; bDBS=57; k=1 | ⊕⊕⊕⊖ | 74.5% | uDBS: 78.9% bDBS: 74.5% | MRgFUS vs uDBS: 3.4% MRgFUS vs bDBS: 0.0% | No significant difference |
| CRST Part C, 12 months | MRgFUS=15; uDBS=13; bDBS=57; k=1 | ⊕⊕⊕⊖ | 88.4% | uDBS: 83.1% bDBS: 85.4% | MRgFUS vs uDBS: 5.3% MRgFUS vs bDBS: 3.0% | No significant difference |
| QUEST, 12 months | MRgFUS=15; uDBS=13; bDBS=57; k=1 | ⊕⊕⊕⊖ | 68.0% | bDBS: 72.0% | MRgFUS vs bDBS: 4.0% | No significant difference |
| Indirect treatment comparison | | | | | | |
| Total CRST, 12 months | MRgFUS= 48 DBS=97; k=3 | ⊕⊖⊖⊖ | NA | NA | MAIC ^a : 0% (0) STC ^a : 0.31% (-2.53 to 3.16) | No significant difference |
| CRST Part C, 12 months | MRgFUS=48 DBS=28; k=2 | ⊕⊖⊖⊖ | NA | NA | MAIC ^a : 0% (0) STC ^a : -4.35% (-12.82 to 4.13) | No significant difference |
| Naïve comparison | | | | | | |
| Total CRST, 12 months | MRgFUS=147; k=6 DBS=215; k=2 | ⊕⊖⊖⊖ | 56.5% | 55.1% | 1.4% | No significant difference |
| CRST Part C, 12 months | MRgFUS=59; k=3 DBS=97; k=1 | ⊕⊖⊖⊖ | 68.2% | 71.4% | 3.2% | No significant difference |

Source: Table 2, pp23-24 of the ADAR

Abbreviations: k= study number; bDBS, bilateral DBS; CRST, clinical rating scale for tremor; DBS, deep brain stimulation; MAIC, Matching-Adjusted Indirect Comparisons; MRgFUS, magnetic resonance-guided focused ultrasound; NA, not applicable; QUEST, quality of life in essential tremor; STC, Simulated Treatment Comparison; uDBS, unilateral DBS;

^a GRADE Working Group grades of evidence (Guyatt et al., 2013)

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect. ⊕⊕⊕⊖ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. ⊕⊕⊖⊖ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. ⊕⊖⊖⊖ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

The ADAR noted that no minimum clinically important difference (MCID) had been established for any of the tremor scales. In the pre-ESC response, the applicant highlighted that Elbe et al 2013⁷ (cited in the [Ratified PICO](#), p12) was unable to specify a MCID. The applicant also considered that as MSAC previously recommended reimbursement of DBS in ET ([Application 1109](#)) then it is already accepted that the differences before and after treatment with DBS are clinically meaningful. Further, the applicant considered that the ITC

⁷ Elble R, Bain P, João Forjaz M, Haubenberger D, Testa C, Goetz CG, Leentjens AF, Martinez-Martin P, Pavy-Le Traon A, Post B, Sampaio C. Task force report: scales for screening and evaluating tremor: critique and recommendations. *Movement Disorders*. 2013 Nov;28(13):1793-800

demonstrated that MRgFUS has a similar level of effectiveness on tremor as DBS. It therefore follows MRgFUS is providing a clinically important benefit to patients.

MRgFUS vs. BSC

A summary of the key outcomes reported in the pivotal sham-controlled trial is presented in Table 9. The ADAR considered that MRgFUS was shown to be statistically superior to sham across all outcomes in the pivotal RCT with significantly greater reductions observed in total CRST, upper limb tremor; tremor-related disability (CRST Part C) and quality of life (QUEST) with an incremental improvement of 44.8%, 47.0%, 60.0% and 45.7%, respectively (p<0.001). The treatment effects observed in the pivotal trial were shown to sustained over the long-term with a 52.7%, 54.3% and 44.8% improvement in hand tremor, disability and quality of life at the 3-year follow-up assessment.

The ADAR considered that these data are supported by the non-comparative studies showing a consistent reduction in the same reported outcomes across all relevant studies included in the assessment with an overall reduction of 57.9% (range: 50.4% - 67.3%) in total CRST; 69.2% reduction in hand tremor (range: 42.4% - 80.5%); 69.0% reduction in CRST Part C (range: 55.1% - 85.0%) and a 63.0% improvement in tremor-related quality of life (range 55.2% - 67.6 %).

Table 9 Balance of clinical benefits and harms of MRgFUS, relative to Sham, and as measured by the critical patient-relevant outcomes in the randomised controlled trial

| Outcomes (units) Follow-up | Participants (studies) | Quality of evidence (GRADE) | Mean difference | Reduction with MRgFUS | Reduction with Sham | Comments |
|-------------------------------|-------------------------------|--------------------------------------|--------------------|-----------------------------|---------------------------|---|
| Total CRST, 12 months | MRgFUS = 56 Sham = 20; k=1 | ⊕⊕⊕⊕ | 38.5% | 40.9% | 2.4% | Statistically favours MRgFUS (p<0.0001) |
| Hand tremor, 12 months | MRgFUS = 56 Sham = 20; k=1 | ⊕⊕⊕⊕ | 47.0% | 47.2% | 0.16% | Statistically favours MRgFUS (p<0.0001) |
| CRST Part C, 12 months | MRgFUS = 56 Sham = 20; k=1 | ⊕⊕⊕⊕ | 60.0% | 62.8% | 2.8% | Statistically favours MRgFUS (p<0.0001) |
| QUEST, 12 months | MRgFUS = 56 Sham = 20; k=1 | ⊕⊕⊕⊕ | 42.5% | 45.7% | 3.2% | Statistically favours MRgFUS (p<0.0001) |

Source: Table 3, p25 of the ADAR

Abbreviations: k= study number; CRST, clinical rating scale for tremor; MRgFUS, magnetic resonance-guided focused ultrasound; QUEST, quality of life in essential tremor;

^a GRADE Working Group grades of evidence (Guyatt et al., 2013)

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect. ⊕⊕⊕⊕ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. ⊕⊕⊕⊕ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. ⊕⊕⊕⊕ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Clinical claim

MRgFUS vs. DBS

The ADAR considered that on the basis of the benefits and harms reported in the evidence base (summarised above), it is suggested that, relative to DBS, MRgFUS has non-inferior safety and non-inferior effectiveness; relative to BSC, MRgFUS has inferior safety yet superior effectiveness. The commentary considered that the clinical claim for safety may need to be revised to uncertain.

MRgFUS vs. BSC

The ADAR considered that on the basis of the benefits and harms reported in the evidence base (summarised above), it is suggested that, relative to BSC, MRgFUS has inferior safety and superior effectiveness. The commentary considered this was reasonable.

Translation issues

The translation issues as summarised by the commentary are shown in Table 10.

Table 10 Summary of translation issues

| Translation type | Translation issue | Summary |
|------------------|--|--|
| Transformation | Adverse event profile transformed to QALYS | <p>The ADAR provided the adverse event profile of MRgFUS and DBS from selected studies and concluded that:</p> <ul style="list-style-type: none"> MRgFUS is potentially associated with a higher risk of short-term and long-term paraesthesia than DBS. MRgFUS, but not DBS, is associated with a short-term intraprocedural risk of MRI burn, headache, lightheaded/dizziness, nausea/vomiting and flushed warmth. DBS, but not MRgFUS, is associated with a risk of infection, hardware complications (e.g. lead erosion) and haemorrhage. <p>Overall, the ADAR concluded: any QALY gains/losses for a given AE is expected to be offset by QALY losses/gains for another AE as demonstrated in the cost-effectiveness analysis reported in Ravikumar 2017, and this justified a cost-minimisation approach, rather than a cost-effectiveness, as recommended by PASC.</p> <p>The commentary considered that as the utility instruments used by Ravikumar et al (2017) vary in sensitivity, and the incremental gain in benefit for MRgFUS is marginal (0.06), as reported by Ravikumar et al (2017), there is uncertainty in either direction of any incremental gains in benefit. However, any change in incremental benefit, for either intervention or comparator, is unlikely to change the overall output significantly.</p> |
| Extrapolation | Extrapolation of treatment effect | <p>The pivotal trial (Elias et al., 2016) shows treatment effect over 3 years. However, the economic model has a time horizon of 10 years. Therefore, it was necessary to demonstrate the adverse event profile at three years was similar to the adverse event profile at 10 years. The ADAR provided evidence to support treatment effect (and not adverse event profile) up to 5 years for MRgFUS and 6 years for DBS.</p> <p>The commentary considered that while evidence was not available between 6 and 10 years for the treatment effect, the treatment effect profiles of both MRgFUS and DBS did not significantly increase over time. More importantly, the safety profile of MRgFUS and DBS appear to be transient and not persistent and therefore are expected to be not significant over the longer term. However, without further evidence, there still is some uncertainty in the extrapolation of safety effects.</p> |

Source: Table 9 of the Commentary

12. Economic evaluation

The ADAR presented a cost-minimisation analysis (CMA) [Table 11] as most differences in safety profiles are transient events and it was not possible to quantify all adverse events with certainty. The ADAR has used the cost-effectiveness study by Ravikumar et al. (2017)⁸ as a proxy to quantify the difference between the two treatments when combining all relevant adverse events, as discussed above in Table 10.

⁸ Ravikumar VK, Parker JJ, Hornbeck TS, Santini VE, Pauly KB, Wintermark M, Ghanouni P, Stein SC, Halpern CH. Cost-effectiveness of focused ultrasound, radiosurgery, and DBS for essential tremor. *Mov Disord*. 2017 Aug;32(8):1165-1173.

Table 11 Summary of the economic evaluation

| | |
|-----------------------------|---|
| Perspective | Health care system |
| Comparator | Deep brain stimulation |
| Type of economic evaluation | Cost-minimisation analysis |
| Sources of evidence | Elias (2016), Huss (2015), Halpern (2019) |
| Time horizon | 10 years |
| Outcomes | Markov model |
| Health states | Alive and Dead |
| Cycle length | Annual |
| Discount rate | 5% |
| Software packages used | Excel |

Source: Table 76, p 172 of the ADAR 1614

The ADAR claims the CMA are based on a number of conservative assumptions:

- The AE profile of MRgFUS could translate to net QALY gains and have greater mortality advantages [based on Ravikumar et al. (2017)]
- Safety costs are excluded which may favour MRgFUS
- The estimate of battery life for DBS may be underestimated
- Recurrence in DBS patients were not included (in favour of MRgFUS)
- Capital costs may have been overestimated for MRgFUS due to conservative estimates of forecasting number of patients
- Medical services associated with MRgFUS may have been overestimated, as it is likely that only two physicians would be required rather than the three physicians used in the costing.
- The total cost of DBS in this assessment was less than the total cost estimated in [MSAC 1109](#).

The ADAR determined the total cost for unilateral DBS separately to the total cost for bilateral DBS. The ADAR determined that 95% of DBS surgeries would be bilateral DBS based on medicare statistics data (the comparison of MBS item 40850 – unilateral and MBS item 40851 - bilateral). The ADAR weighted the total cost of unilateral and bilateral DBS to compare with the total cost of MRgFUS (Table 12).

Table 12 Comparison of costs (discounted) associated with MRgFUS vs. DBS over a 10-year time horizon

| | MRgFUS | Weighted DBS ^a | Unilateral DBS | Bilateral DBS |
|--|-------------------|---------------------------|------------------|------------------|
| Primary procedure | \$43,142 | \$59,028 | \$42,420 | \$59,985 |
| Prostheses/consumable costs | \$Redacted | \$16,427 | \$31,583 | \$12,000 |
| Medical service costs | \$Redacted | \$4,892 | \$7,301 | \$8,082 |
| Hospitalisation costs | \$Redacted | \$21,101 | \$21,101 | \$2,110 |
| Capital costs | \$Redacted | - | - | \$20,950 |
| Retreatment | \$2,058 | - | - | - |
| Battery replacement | - | \$12,007 | \$12,193 | \$11,997 |
| Device programming | - | \$2,295 | \$2,161 | \$2,303 |
| Total cost | \$45,201 | \$73,330 | \$56,774 | \$74,284 |
| Incremental cost (relative to MRgFUS) | - | -\$28,130 | -\$11,574 | -\$29,083 |

DBS, deep brain stimulation; MRgFUS, magnetic resonance-guided focused ultrasound
Source: Table 12 of the Commentary

The model is most sensitive to DBS length of stay (shorter period favours DBS), time horizon (shorter period favours DBS) and MRgFUS utilisation (less utilisation favours DBS). The commentary considered that the sensitivity analysis provided in the ADAR provides adequate justification and certainty that the total cost for MRgFUS would be less than DBS.

13. Financial/budgetary impacts

The ADAR used a mixed-methods approach using multiple sources of data was to estimate MBS-funded MRgFUS patients. This reflected MBS data limitations and the expected sources of patients from different hospital settings. The financial implications to the MBS resulting from the proposed listing of MRgFUS are summarised in Table. The commentary made several minor revisions (removal of re-treatment [i.e. primary procedures only included], changes to MBS schedule fees and reversion of proposed fee for one item reverted to amount agreed in the Ratified PICO) to the ADAR analysis had a moderate effect, decreasing the estimated 5-year MBS net financial impact from \$1.45 million to \$1.23 million.

Table 13 Total costs to the MBS associated with MRgFUS

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|----------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| MRgFUS procedures ^a | 58 | 59 | 60 | 60 | 60 |
| Substituted DBS procedures | 12 | 12 | 12 | 12 | 12 |
| MRgFUS services | - | - | - | - | - |
| Total cost | \$456,525 <i>\$414,515</i> | \$464,156 <i>\$414,515</i> | \$471,787 <i>\$414,515</i> | \$471,787 <i>\$414,515</i> | \$471,787 <i>\$414,515</i> |
| -to MBS | \$352,813 <i>\$317,442</i> | \$358,711 <i>\$317,442</i> | \$364,608 <i>\$317,442</i> | \$364,608 <i>\$317,442</i> | \$364,608 <i>\$317,442</i> |
| -to patients | \$103,712 <i>\$97,074</i> | \$105,446 <i>\$97,074</i> | \$107,179 <i>\$97,074</i> | \$107,179 <i>\$97,074</i> | \$107,179 <i>\$97,074</i> |
| Changes to other services | | | | | |
| Total costs offsets | -\$88,201 <i>-\$88,448</i> | -\$90,369 <i>-\$90,864</i> | -\$92,537 <i>-\$93,279</i> | -\$96,490 <i>-\$97,232</i> | -\$98,905 <i>-\$99,647</i> |
| -to MBS | -\$67,165 <i>-\$67,375</i> | -\$69,008 <i>-\$69,428</i> | -\$70,851 <i>-\$71,482</i> | -\$74,058 <i>-\$74,689</i> | -\$76,112 <i>-\$76,743</i> |
| -to patients | -\$21,036 <i>-\$21,073</i> | -\$21,361 <i>-\$21,435</i> | -\$21,685 <i>-\$21,797</i> | -\$22,431 <i>-\$22,543</i> | -\$22,793 <i>-\$22,904</i> |
| Net financial impact | | | | | |
| Total costs | \$368,324 <i>\$326,067</i> | \$373,787 <i>\$323,652</i> | \$379,251 <i>\$321,237</i> | \$375,298 <i>\$317,284</i> | \$372,883 <i>\$314,868</i> |
| -to MBS | \$285,648 <i>\$250,067</i> | \$289,703 <i>\$248,013</i> | \$293,757 <i>\$245,960</i> | \$290,550 <i>\$242,753</i> | \$288,496 <i>\$240,699</i> |
| -to patients | \$82,676 <i>\$76,000</i> | \$84,085 <i>\$75,639</i> | \$85,494 <i>\$75,277</i> | \$84,748 <i>\$74,531</i> | \$84,386 <i>\$74,169</i> |

Source: Compiled from Table 6, p28 of ADAR and Table 13 of the Commentary

Abbreviations: DBS, deep brain stimulation; MBS, Medicare Benefits Schedule; MRgFUS, magnetic resonance-guided focused ultrasound

^a 57 primary procedures performed per year

Note, the Commentary's estimates in italics assumed primary procedures only, the cost of the proposed item for MRI and stereotactic anatomic localisation is as per the Ratified PICO, not the revised cost used in the ADAR (i.e., \$336.00 instead \$994.60) and updated MBS Schedule fees as at November 2020.

The ADAR estimated 57 MRgFUS patients per annum in the first five years, with 12 of these switching from DBS treatment and 45 from otherwise privately funded MRgFUS treatment.

The commentary considered there was uncertainty in this estimate, with the potential number of patients potentially underestimated as a result of uncertainty regarding:

- the proportion of ET patients treated in an ‘MBS setting’
- switching rates of DBS patients
- the likely eligible patient population of patients with severe, medically-refractive ET, including those currently on BSC or sub-optimal pharmacotherapy, and the potential for MBS listing to ‘bring forward the market’ for active second-line treatment
- The likely number of privately-funded MRgFUS patients otherwise being treated.

The commentary also noted that DBS utilisation on the MBS has not grown since 2010 (Figure 31 of the ADAR p 203), however the ADAR estimates that 25% of DBS patients are treated for ET, based on the assumption that the proportion of patients treated with DBS in the private healthcare system is equivalent to the proportion of patients treated in the public healthcare system. However, the commentary considered it is likely that DBS surgery has a higher prevalence in the private system than the public system.

Furthermore, the commentary considered that the MBS listing of MRgFUS has the potential to ‘grow the market’ for ET treatment, with potential financial implications for the MBS. Additional analysis should be undertaken, in particular to consider the likely eligible patient population and MRgFUS treatment uptake.

In the pre-ESC response, the applicant highlighted that its budget impact included growth of the MBS market as a result of MRgFUS listing. Specifically, it is estimated 90% of current MRgFUS use across the two Australian institutions which it is available (St Vincent’s Hospital Sydney and Future Medical Imaging Group Centre Melbourne) will shift to an MBS treatment setting, resulting in the MBS funding an additional 45 procedures for ET annually.

Private Health Insurers

The ADAR estimated the financial impact of the MRgFUS single-use kit being reimbursed on the Prostheses List at the proposed amount, **\$Redacted**. The same prostheses costs associated with DBS procedures in the economic evaluation were applied in estimating the financial impact to private health insurers of substituting DBS procedures. The Commentary revised the estimates to exclude re-treated patients and reflect reduced DBS treatment numbers reducing the financial impact to private health insurers (see italicised values below in Table 14).

Table 14 Financial impact to private health insurers of listing the MRgFUS kit on the Prostheses List

| Row | | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Source / calculation |
|-------------------|--|--|--|--|--|--|----------------------|
| MRgFUS | | | | | | | |
| A | MRgFUS procedures | 58 57 | 59 57 | 60 57 | 60 57 | 60 57 | Table 98 |
| B | Cost per MRgFUS kit | \$Redacted | \$Redacted | \$Redacted | \$Redacted | \$Redacted | Table 83 |
| C | Total cost to private health insurers | \$Redacted \$Redacted | \$Redacted \$Redacted | \$Redacted \$Redacted | \$Redacted \$Redacted | \$Redacted \$Redacted | A*B |
| DBS | | | | | | | |
| D | Substituted bilateral DBS procedures | 12 | 12 | 12 | 12 | 12 | Table 103 |
| E | Prostheses cost per bilateral DBS | \$31,583 | \$31,583 | \$31,583 | \$31,583 | \$31,583 | Table 85 |
| F | Substituted unilateral DBS procedures | 1 | 1 | 1 | 1 | 1 | Table 103 |
| G | Prostheses cost per unilateral DBS | \$16,427 | \$16,427 | \$16,427 | \$16,427 | \$16,427 | Table 85 |
| H | Substituted bilateral battery replacements | - | - | - | 6 | 6 | D*0.5 ^a |
| I | Prostheses cost per bilateral battery replacement | \$16,329 | \$16,329 | \$16,329 | \$16,329 | \$16,329 | Table 86 |
| J | Substituted unilateral battery replacements | - | - | - | 1 | 1 | F*1 ^a |
| K | Prostheses cost per unilateral battery replacement | \$8,168 | \$8,168 | \$8,168 | \$8,168 | \$8,168 | Table 86 |
| L | Total substituted prostheses costs | \$379,694 | \$379,694 | \$379,694 | \$480,484 | \$480,484 | D*E+F*G+H*I+J*K |
| Net impact | | | | | | | |
| M | Net impact to private health insurers | \$Redacted \$Redacted | \$Redacted \$Redacted | \$Redacted \$Redacted | \$Redacted \$Redacted | \$Redacted \$Redacted | C-L |

Source: Table 59 of the Commentary

Note: Table references refer to the original ADAR.

Rounding errors may apply. See spreadsheet "Section E_MRgFUS".xlsx for complete calculations.

^a Patients are attributed a battery replacement four years after the initial procedure, as detailed in Section D.

Abbreviations: 'DBS'=deep brain stimulation, MRgFUS=magnetic resonance-guided focused ultrasound

14. Key issues from ESC for MSAC

| ESC key issue | ESC advice to MSAC |
|--|--|
| Item descriptor – once per lifetime and unilateral treatment | Reinstate once per lifetime restriction, given that there is limited clinical evidence to support effectiveness and safety of retreatment and contralateral/bilateral MRgFUS. |
| Comparative evidence is limited for MRgFUS vs. DBS | Note that there are no RCT-based data, limited data with small numbers of patients, incorporating different assessments of tremor and limited long-term follow-up of MRgFUS. |
| Item number rewording on eligibility criteria | Consider revising the eligibility and ineligibility criteria so that #2, #3, #5, #6 are similar to #1 and #4. |
| Item descriptor and multiple operation rule | Seek clarification from the Department as to how this will work in practice with three specialists claiming. |
| Fees | Examine the proposed fee for #2 (planning). The clinician fee for the MRgFUS procedure is high compared with the more invasive DBS procedure. |
| Appropriateness of economic model | Note that the claim to inform the type of economic evaluation is based on limited and uncertain comparative evidence, in particular the very different safety profile may justify a CUA (as PASC advised). Furthermore, there were some concerns with the CUA by Ravikumar 2017 resulting in a high level of uncertainty in the transformation of adverse events to quality-adjusted life years (QALYs) used to validate the ADARs CMA approach. |

ESC discussion

ESC noted that this application was for a Medicare Benefits Schedule (MBS) listing of MRI-guided focused ultrasound (MRgFUS) in treatment of medically refractory essential tremor (ET). ESC noted that the applicant intends to lodge a Prostheses List Advisory Committee (PLAC) application for reimbursement of the MRgFUS kit on the Prostheses List.

ESC noted MRgFUS creates an irreversible thalamic lesion, unlike the main comparator, deep brain stimulation (DBS), which is fully-reversible. ESC noted the secondary comparator was best supportive care (BSC), given in a subgroup of the proposed population contraindicated or not suitable for surgery.

ESC noted that there was no consumer feedback for this application. ESC noted consumer issues relating to there being no consensus on the definition of medically refractory ET which may result in inconsistent interpretation, concerns regarding patient safety, in particular no evidence for retreatment and salvage treatment, and that some patients have prolonged recovery which may affect patient after care.

ESC noted that there are only two centres in Australia that offer this treatment (in Sydney and Melbourne), which raises concerns around equity of access.

ESC noted that there are six item descriptors:

- #1 – MRI for pre-surgical suitability (Table 2)
- #2 – MRI for pre-surgical planning (Table 3)
- #3 – Treatment/intraoperative procedure by the neurologist (Table 4)
- #4 – Treatment/intraoperative procedure by the neurosurgeon (Table 5)
- #5 – Treatment/intraoperative procedure by the interventional radiologist (Table 6)
- #6 – MRI for post-surgical assessment (Table 7).

ESC noted that the applicant removed the “claimable once per patient per lifetime” from the item descriptors for the intraoperative procedure (#3, #4, #5) as per the Ratified PICO, so as to allow retreatment and contralateral treatment. ESC also noted the applicant-developed assessment report (ADAR) included in tremor recurrence to allow for retreatment in the algorithm. ESC considered the advice in the pre-ESC response from a clinical expert (1 neurosurgeon) supporting retreatment on the basis that the clinician would be judicious in retreatment, the clinician loses autonomy if no retreatment option, technical failure can very occasionally occur, the safety profile is unlikely to be altered in a retreatment population, excluding retreatment is unlikely to provide any substantial savings, and patients may need to seek alternative options, most likely DBS. However, ESC noted that the applicant acknowledges that “none of these studies report clinical outcomes in patients receiving retreatment, and that there is very little evidence for the efficacy/safety of retreatment” (pre-ESC response, p1). ESC also noted that the applicant acknowledges that treatment of the contralateral side is currently investigational and that there is currently no data on contralateral treatment, although trials are underway. Thus, ESC considered that the item descriptor should be restricted to unilateral, once-only treatment.

ESC noted that the proposed MBS items for pre-surgical suitability assessment (#1) and for the neurosurgical services (#4) are restricted to patients who do not have a primary diagnosis of Parkinson’s disease, with the exception of patients with a primary diagnosis of ET with parkinsonian features consistent with the definition of ET plus. ESC considered it is unclear why the other proposed MBS items (pre-surgical planning, neurology services and radiology services) do not include this restriction. ESC considered that this inconsistency in the eligibility criteria between the six items should be addressed.

ESC noted that the ratified PICO implies that neurosurgeons are the only specialists delivering the procedure component, but that this is not clear in the algorithm given interventional radiologists can also provide this procedure alongside neurosurgeons. ESC also noted that the multiple operation rule applies to Group T8, which – in this case – is the neurosurgeon only. ESC recommended seeking clarification from the Department as how the item will work if there are three specialists claiming.

ESC queried the fee for #2 (\$994.60), which is higher than the estimate in the Ratified PICO (\$336). ESC noted the pre-ESC response that the fee includes a component derived from MBS item 40800 which is \$658 – stereotactic anatomical localization required for target verification – but that this item number has been discontinued. ESC also queried the fee justification for the procedure based on DBS, as MRgFUS is less invasive procedure than DBS.

ESC noted that the clinical data for MRgFUS vs. DBS consisted of two retrospective comparative studies, an indirect treatment comparison and a naïve comparison of non-comparative MRgFUS and DBS studies, with no direct head-to-head randomised controlled studies (RCTs). For MRgFUS vs. BSC, ESC noted the pivotal evidence was a sham controlled RCT (Elias et al. 2016).

In terms of comparative safety of MRgFUS vs. DBS, ESC noted that intra-procedural adverse events (AEs) were only relevant for MRgFUS with the most common including dizziness, headache, nausea and vomiting and that these resolve. ESC also noted AEs related to the stereotactic frame were reported. ESC noted for MRgFUS post-procedural AEs included paraesthesia and gait disturbance, but these tended to be either transient or improve within 12 months. ESC noted DBS has a different safety profile with AEs including balance or gait difficulties and speech disturbance, with some resolving after hardware programming. ESC

also noted that wound infections at the implant site and other complications related to the DBS hardware were reported, some requiring hardware replacement over time. ESC noted that the ADAR claimed that there is a different yet non-inferior safety profile. However, ESC agreed with the commentary who considered that there is an uncertain safety profile, and that meaningful comparison is difficult due to the different safety profile.

In terms of comparative effectiveness of MRgFUS *vs.* DBS, ESC agreed with the commentary who considered that both procedures appear to be effective at significantly reducing tremor (total and hand tremor), tremor-related disability and improving quality of life, at least in short to medium term (up to 4 years of follow-up for MRgFUS). ESC considered that the ADARs clinical claim of non-inferior effectiveness may be appropriate. ESC noted there is consistency across the whole body of evidence; however, this is based on limited and low-quality comparative evidence (no direct RCT), small patient numbers, different methods of assessment of tremor severity, limited long-term follow-up of MRgFUS and no minimum clinically important difference (MCID) has been established and validated for ET.

ESC considered the secondary comparison of MRgFUS *vs.* BSC noting that the ADARs claim was inferior safety and superior effectiveness. ESC agreed with the commentary who considered this was reasonable.

ESC noted that only an economic evaluation was presented of MRgFUS *vs.* DBS, which was appropriate. ESC noted that the applicant used a cost-minimisation analysis (CMA) approach based on the clinical claim of non-inferiority. However, ESC questioned whether that claim is justified, especially regarding safety, noting that each intervention has a different safety profile. Thus, ESC considered a cost-utility analysis (CUA) might be more appropriate, as requested by PASC. Furthermore, ESC noted that the applicant justifies the CMA approach based on the outcomes of a model-based CUA by Ravikumar 2017, but there are some concerns with this study:

- The model was a decision tree using aggregated health states (representing major and minor complications) which can impact precision of modelled outputs
- The model inputs were informed from (simple) pooled data reporting treatment-related complications
- Of note, the utility values associated with complications were derived from different instruments and thus it is difficult to conclude if the utilities used in the model-based evaluation are valid and generalisable.

Overall, ESC considered that the transformation of AEs to QALYs was uncertain, and thus the claim of negligible incremental QALYs to support the CMA approach adopted by the ADAR. ESC also noted the results of small (0.06) net QALY gain from Ravikumar 2017 was inconsistent to a published Ontario health technology assessment reporting that in the base-case model MRgFUS was less effective (QALY loss of 0.25 over 5 years) but cost saving, and thus would be in the south-west quadrant of the cost-effectiveness plane.

ESC considered the ADARs CMA using a Markov model to estimate the long-term (10 year) health care resource utilisation between MRgFUS and DBS. ESC considered that the level of details and cost items included in the costing model are appropriate, including the assumptions which were mainly conservative (in favour of DBS). ESC also considered that the sensitivity analyses provide adequate certainty that the total cost for MRgFUS would be less than DBS. Thus, ESC considered that the estimated cost savings appear to be reasonable, if the clinical claim of non-inferiority is supported by MSAC. However, ESC noted that there is some uncertainty regarding sustained benefits, given that there is limited long-term data.

ESC also noted that a published CMA (Igarashi et al. 2019) excluding safety costs (similar to ADAR) reported cost savings with MRgFUS compared with unilateral DBS.

ESC noted that in the ADARs financial model including retreatment, the net cost to MBS for MRgFUS is expected to be ~\$285,000 in year 1 and \$288,000 in year 5. However, ESC noted some concerns with how MRgFUS use was estimated from a number of assumptions:

- The ADAR assumed only 20% of existing DBS-treated patients would annually switch to MBS (underestimate)
- The ADAR assumed 90% of current privately funded MRgFUS would switch to MBS (underestimate)
- The ADAR assumed 1.7% annual rate for retreatment.

However, ESC also noted that the commentary's revised financial estimates removing retreatment and updating MBS costs only had a small impact. ESC also considered that it was unclear how many ET patients would choose a non-invasive, irreversible MRgFUS procedure, especially those for whom surgery was previously declined. Overall, ESC considered the methods and data sources were appropriate, but the ADAR underestimated the budget impact, with some uncertainty remaining whether the MBS funding of MRgFUS will "grow the market".

ESC also noted the commentary removed retreatment and reduced DBS treatment numbers to estimate the financial impacts of the prostheses (MRgFUS kit) to private health insurers.

ESC queried whether robust evidence on clinical benefits and cost-effectiveness is likely to emerge, and noted that there is a multi-centre, international observational registry to assess the effectiveness of MRgFUS neurosurgery in people with various neurologic disorders such as ET and Parkinson's movement disorders, or neuropathic pain ([NCT03100474](#); estimated enrolment = 500 participants. The primary outcome is the CRST, target follow-up duration is 5 years, and the estimated study completion in 2024 (primary completion date: January 2021).

15. Other significant factors

Nil.

16. Applicant comments on MSAC's Public Summary Document

The applicant is clearly disappointed with MSAC's recommendation. In particular, we believe the conclusion "evidence is very poor for MRgFUS" is not necessarily a fair reflection of the MRgFUS clinical trial program relative to DBS. The evidence for MRgFUS includes a well conducted, multi-centre, double-blind randomised controlled trial (Elias et al. 2016) whereas the evidence for DBS includes no such comparative studies. The safety of MRgFUS is well established (Fishman et al. 2018) whilst the safety of the invasive DBS procedure and ongoing risk of device related failures does not appear to have been given similarly critical consideration. MRgFUS has been recommended for reimbursement in healthcare systems around the world including Israel, UK, Germany, Switzerland, Italy and Japan. The applicant is disappointed what MSAC's decision means for patients without private health insurance who do not have access to DBS without substantial out of pocket expenses. With this in mind, Insightec will continue to work with the Department of Health and MSAC to address their concerns and secure reimbursement of this important treatment option for patients with medically refractory essential tremor.

17. Further information on MSAC

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