



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1614.1 – Magnetic resonance-guided focused ultrasound for the treatment of medically refractory essential tremor

Applicant: Insightec

Date of MSAC consideration: 31 March – 1 April 2022

1. Purpose of application

A resubmission requesting Medicare Benefits Schedule (MBS) listing of magnetic resonance-guided focused ultrasound (MRgFUS) for the treatment of 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 supported the creation of new MBS items for MRgFUS for the treatment for medically refractory ET. MSAC noted limitations in the clinical evidence but accepted that MRgFUS meets an unmet need, had a different but acceptable safety profile and had non-inferior effectiveness and acceptable cost-effectiveness compared with MBS-funded deep brain stimulation (DBS). MSAC advised its support was provided only if a suitable set of item descriptors and fees can be agreed upon.

MSAC was concerned there may be high out of pocket costs to consumers as it was unclear whether the cost of certain device consumables used with the procedure could be covered by the Prostheses List.

Consumer summary

MSAC noted that this application from Insightec Ltd was a resubmission requesting Medicare Benefits Schedule (MBS) listing of magnetic resonance-guided focused ultrasound (MRgFUS) for the treatment of medically refractory essential tremor.

Essential tremor is a chronic, progressive condition that affects the neurological system (the nerves and nervous system). It is characterised by involuntary, rhythmic, back-and-forth tremors, usually of the arms, hands or fingers, that does not have an underlying cause (e.g. Parkinson's disease). Severe cases of essential tremor can significantly impact everyday life, affecting a person's ability to eat, perform household activities and function in the workplace. It can be treated with deep brain stimulation, which is an invasive operation on the brain (i.e. a form of surgery) but not everyone responds to this treatment. Also, some people cannot, or do not want to undergo brain surgery.

Consumer summary

MRgFUS is a non-invasive (i.e. non-surgical), one-step method to treat essential tremor that has not responded to treatment (i.e. is medically refractory). It combines magnetic resonance imaging (MRI) and ultrasound pulses to heat and only destroy a specific area of brain tissue that is the source of tremor (the ventralis intermediate nucleus of the thalamus). This interrupts the abnormal activity associated with essential tremor.

Despite the limitations of existing clinical evidence allowing for direct comparisons between MRgFUS and deep brain stimulation surgery on safety and effectiveness, MSAC recognised that MRgFUS addressed an unmet clinical need, as it provides patients with the choice of a procedure that is more effective than best supportive care, but less invasive and just as effective as deep brain stimulation surgery, but with a different pattern of safety concerns. MSAC also acknowledged that MRgFUS had acceptable cost-effectiveness compared with deep brain stimulation surgery.

However, MSAC advised that the proposed item descriptors and fees need further refinement and justification before it could be listed. It also questioned who would pay for the high cost of consumables for the procedure which comprise a significant proportion of the procedure's costs given that these consumables will not attract a Medicare rebate and may not attract a private health insurance rebate if they are not covered by the Prostheses List.

MSAC's advice to the Commonwealth Minister for Health

MSAC supported the creation of new MBS items for MRgFUS for the treatment of medically refractory essential tremor. Noting limitations in the clinical evidence, MSAC accepted that it was unlikely that better evidence would be available in the future and therefore accepted that MRgFUS addressed an unmet clinical need, and was at least as effective and cost-effective as surgery, with an acceptable safety profile concerns. However, MSAC advised this support was provided only if a suitable set of item descriptors and fees could be agreed on, which would need to be resolved through the MSAC Executive. MSAC was concerned there may be high out of pocket costs to consumers due to it was unclear whether the cost of certain consumables used with MRgFUS could be covered by the Prostheses List.

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

MSAC noted this application from Insightec Ltd was a resubmission requesting MBS listing of MRgFUS for the treatment of medically refractory ET. MSAC recalled that the previous submission considered in April 2019, it accepted that there was an unmet clinical need for a non-invasive intervention (i.e. a non-surgical intervention) compared with MBS-funded DBS, but did not support the application because of the evidence for comparative safety (including that adverse events for MRgFUS were only short-term) was too uncertain and – as a consequence – the economic evaluation was inappropriate. In addition, 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.

MSAC noted the population, comparators and clinical management algorithm were all unchanged in the resubmission (with DBS as the main comparator and BSC as a secondary comparator). MSAC noted retreatment and contralateral treatment with MRgFUS were excluded in the resubmission through the inclusion of a once per lifetime limit on the number of treatments per patient.

MSAC noted that consultation feedback for the resubmission was only received from a single consumer, which was strongly supportive of the application. This feedback highlighted the detrimental effects of having suffered tremors for approximately 15 years, and that after receiving MRgFUS could return to work, had much improved selfcare and enjoying social

interaction again – this patient labelled MRgFUS “a medical miracle”. Other benefits included a short recovery time, no overnight stay in hospital, and reduced medication and associated costs.

MSAC recalled that it had advised that the resubmission should have a packaged item, rather than six separate items within one application (however, MSAC acknowledged that the Department had sought a breakdown of the services to better define which service would be provided by which speciality). MSAC noted that in the resubmission the applicant had removed the item number and fee for treatment by a radiologist (item 5 in the previous submission), but that little else had changed from the previous submission (outside of precluding retreatment and contralateral treatment through the inclusion of a once per lifetime limit on the number of treatments per patient).

MSAC noted the pre-MSAC response which responded to the ESC issues for the item descriptors, but considered that there are several issues that still need to be resolved. For magnetic resonance imaging (MRI) for pre-surgical suitability assessment, MSAC questioned the need for this item given that many patients would have likely already had at least one MRI as part of current standard of care. MSAC queried whether these existing MRI images could be used (if of good quality) and also whether there should be any requirement on how recent a previous MRI may need to be; MSAC advised the Department could consult with the relevant experts (e.g. RANZCR) to resolve these matters. MSAC also considered that the MRI item for pre-surgical suitability assessment should be restricted to a once per lifetime, which was also acknowledged by the applicant in the pre-MSAC response. For MRI for pre-surgical planning, MSAC considered that it is likely to require a longer scan time and different expertise from the MRI for pre-surgical suitability. MSAC considered whether the items for pre-surgical planning and treatment by a neurosurgeon could be packaged into a single item though it acknowledged that the item for pre-surgical suitability, if it were to remain, should be a separate item. MSAC questioned the exact roles of the practitioners for the items for pre-surgical planning (by a radiologist), intra-operative procedure (by a neurosurgeon) and intra-operative procedure (by a neurologist). MSAC considered that the post-surgical MRI may be more to demonstrate the induced thalamic lesion and prognosis rather than management change. MSAC questioned whether the post-surgical MRI could be optional and made available under current MBS funding arrangement (rather than being part of the treatment package), as it may not be necessary for patients who are doing well and have no adverse events (AEs).

MSAC considered the fees for the separate items for treatment by the neurosurgeon and neurologist to be very high and not adequately justified. MSAC considered the fees should depend on the length of the procedure, as all specialists are trained to a level of expertise, and should be calculated according to a comparative time-based structure. MSAC advised that more justification was needed for these fees. MSAC also considered that the same provider (e.g. neurosurgeon) should not be able to claim for both treatment items.

MSAC considered that consultation with the relevant experts regarding the matters identified for the item structure, and fees would be needed. MSAC also noted the Department’s advice regarding the training component of the service. Overall, MSAC advised that the item descriptors, fees and training matters could be resolved through the MSAC Executive. The item descriptors and fees reflecting the MSAC advice are presented below:

MBS item descriptor – pre-surgical suitability assessment- the need for this item and structure to be confirmed at the MSAC Executive

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> <p>Assessment of suitability for treatment of essential tremor with MRI-guided focused ultrasound Essential tremor where:</p> <p>(a) Symptoms cause severe disability, and (b) Tremor has proven refractory to, or recurred following, maximal medical therapy</p> <p>The service is not applicable to patients with a primary diagnosis of Parkinson's disease^a Bulk bill incentive (Anaes.) Claimable only once per patient per lifetime</p>
MBS Fee: \$403.20 Benefit: 75% = \$302.40 85% = \$342.75

MBS item descriptor – pre-surgical planning- the item structure and fee to be confirmed at the MSAC Executive

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>
MBS Fee: \$994.60 Benefit: 75% = \$745.95 85% = \$845.41 To be confirmed at the MSAC Executive

MBS item descriptor – treatment/intraoperative procedure (neurology services) - the item structure and fee to be confirmed at the MSAC Executive

Category 3 – THERAPEUTIC PROCEDURES
<p>MRI-GUIDED FOCUSED ULTRASOUND (unilateral), target localisation incorporating anatomical and physiological techniques, including intraoperative clinical evaluation Multiple Operation Rule (Anaes.) (Assist.) Claimable only once per patient per lifetime.</p>
MBS Fee: \$2,055.05 Benefit: 75% = \$1,541.29 To be confirmed at the MSAC Executive

MBS item descriptor – Treatment/intraoperative procedure (neurosurgery services) - the item structure to be confirmed at the MSAC Executive

Category 3 – THERAPEUTIC PROCEDURES
<p>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:</p> <p>Essential tremor where:</p> <p>(a) Symptoms cause severe disability, and</p> <p>(b) Tremor has proven refractory to, or recurred following, maximal medical therapy</p> <p>The service is not applicable to patients with a primary diagnosis of Parkinson’s disease^a</p> <p>Multiple Operation Rule (Anaes.) (Assist.)</p> <p>Claimable only once per patient per lifetime</p>
<p>MBS Fee: \$3,165.50 Benefit: 75% = \$2,372.62b To be confirmed at the MSAC Executive</p>

MBS item descriptor – Post-surgical treatment assessment- the need for this item and structure to be confirmed at the MSAC Executive

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> <p>Assessment of treatment outcomes following MRI-guided focused ultrasound procedure</p> <p>Bulk bill incentive (Anaes.)</p> <p>Claimable only once per patient per procedure</p>
<p>MBS Fee: \$403.20 Benefit: 75% = \$302.40 85% = \$342.75</p>

MSAC noted the resubmission identified new, but mostly low-level, evidence from clinical trials, including five single-arm studies for MRgFUS, one unpublished 5-year follow-up of an MRgFUS RCT (original sham control trial by Elias 2016¹; unpublished 5-year follow-up by Cosgrove² expected for completion in December 2022), and one systematic review on outcomes and safety data for MRgFUS versus DBS (Giordano 2020³).

MSAC noted the applicant-developed assessment report (ADAR) resubmission claimed the safety profile of MRgFUS was different, but non-inferior, to that of DBS. For the comparative safety of MRgFUS versus DBS, MSAC noted the new systematic review by Giordano (2020)³, which included 29 studies (covering 1,208 patients, of whom 731 were treated with DBS, 247 being via unilateral DBS and 477 patients were treated with MRgFUS, not including the Cosgrove update), showed an overall complication rate that was similar to the previous submission. MSAC also noted the distribution of AEs remained different between the two techniques – gait disturbance, paraesthesia (particularly in the hand), nausea and persistent AEs were more common for MRgFUS, while speech disturbance and local adverse symptoms (the biggest advantages for MRgFUS treatment) were more common for DBS. MSAC acknowledged that a meaningful comparison of comparative safety was difficult (and the claim of non-inferior safety uncertain) due to differences in the distribution of AEs. MSAC also considered there may never be adequate

¹ Elias WJ, Lipsman N, Ondo WG, Ghanouni P, Kim YG, Lee W et al. (2016). A randomized trial of focused ultrasound thalamotomy for essential tremor. *N Engl J Med*, **375**(8):730–739.

² Cosgrove, GR (2021). Magnetic resonance guided focused ultrasound thalamotomy for essential tremor – long term follow-up results. Not published.

³ Giordano M, Caccavella VM, Zaed I, Foglia Manzillo L, Montano N, Olivi A et al. (2020). Comparison between deep brain stimulation and magnetic resonance-guided focused ultrasound in the treatment of essential tremor: a systematic review and pooled analysis of functional outcomes. *J Neurol Neurosurg Psychiatry*, **91**(12):1270–1278.

evidence to distinguish between risk profiles because they are so different, so informed patient choice might be the best way to determine which is preferred in individual cases.

MSAC noted the new unpublished study by Cosgrove² which provided five year follow up of the Elias randomised sham control trial¹. These results showed that AEs either remained stable or improved over 5 years, while the commentary disagreed and highlighted the result that the ataxia rate doubled (from 1.3% at 3 years to 2.6% at 5 years), although the commentary acknowledged the numbers were small (one patient at 3 years increasing to two patients at 5 years). MSAC also noted the pre-ESC response that the one new case of ataxia was not treatment related – as the patients had neurological issues, ataxia may have occurred regardless. In weighing up these considerations, MSAC agreed with ESC that despite the limited comparative evidence, there was consistency in the results suggesting safety for MRgFUS is sustained up to 5 years.

Regarding comparative effectiveness, MSAC noted the ADAR claimed MRgFUS had non-inferior clinical efficacy compared with DBS. In the previous submission, MSAC had noted concerns that although there was a significant difference in the tremor scales before and after MRgFUS, there was no minimal clinically important difference (MCID) established for these tremor scales in MRgFUS. Therefore, it was not known if the improvement was clinically significant. MSAC noted that the commentary attempted to establish MCID using data already collected; an analysis of MCID using the Clinical Rating Scale for Tremor (CRST) and the Quality of Life in Essential Tremor Questionnaire (QUEST) was provided, looking at the percentage change in tremor score before and after MRgFUS. MSAC noted that this analysis determined that MRgFUS met the 0.5 standard deviation MCID threshold when compared to the sham trial, and on the basis of this appeared to demonstrate a MCID for MRgFUS (the commentary was unable to demonstrate MCID against DBS).

MSAC noted the resubmission included one study from Tsuboi (2020)⁴ on the long-term effectiveness of DBS, where most patients had exclusive ET. This study showed that overall improvements in motor, tremor activities of daily living (ADL) and hand function scores from DBS were sustained for up to 6 years. For the long-term effectiveness of MRgFUS, MSAC noted that the unpublished Cosgrove study included in the resubmission showed improvements from MRgFUS were sustained for up to 36 months post-treatment. While there was some decline, improvements were better than baseline across all domains.

Overall, MSAC agreed with ESC that the clinical claim that MRgFUS is non-inferior to DBS is reasonable, with both procedures being effective for at least 4 years.

MSAC noted that the resubmission addressed the previous MSAC concern regarding comparative safety by including a cost-utility analysis (CUA) comparing MRgFUS with DBS. The resubmission used a CUA that was based on the 2018 Ontario Health Technology Assessment (OHTA) model, adapted for Australian conditions. The CUA used a decision tree and Markov model, and included transient AEs within 1 year of the procedure and long-term AEs. MSAC noted the health state transition probabilities were based on rates of mortality, tremor recurrence and reoperation, with some assumptions applied due to limited data (e.g. recurrence was assumed to be the same between arms, and reoperation if recurrence was assumed to be 40%). MSAC considered the utility estimates of tremor states, used for the modelling of long-term AEs, to be appropriate.

MSAC noted the issues raised by ESC for the model, and that the main uncertainty in the model related to the quantification of adverse events by using an utility adverse event multiplier. MSAC noted that ESC concluded that while the method used to model long-term adverse events does not appear to be conceptually appropriate, it may be sufficient to enable general exploration and establish a broad range of plausible incremental cost-effectiveness ratios (ICERs) to inform MSAC's consideration. MSAC agreed with ESC and considered that any improvements in the

⁴ Tsuboi, T., et al. (2020). "Longitudinal follow-up with Vim thalamic deep brain stimulation for dystonic or essential tremor." *Neurology* 94(10): e1073-e1084.

model will be subject to limitations in the evidence to inform the model inputs, and thus considered it unlikely that the model will be improved by evidence in the foreseeable future.

MSAC noted that from the results of the model of MRgFUS versus DBS, MRgFUS is substantially less costly than DBS but had fewer QALYs (see Table 12), resulting in an ICER in the southwest quadrant (see Figure 1). MSAC considered in this particular case, the reduction in utility was small (and highly uncertain) while the cost savings were considerable (and highly certain). MSAC noted that the key driver of the model was the utility adverse event multiplier for each treatment. MSAC acknowledged the ICER value will change in response to changes in the multiplier but given that it was unlikely that MRgFUS would ever be more expensive than DBS as long as incremental effectiveness was negative, the result would stay in the southwest quadrant (i.e. slightly inferior therapy but at a much lower cost).

MSAC considered that, compared with BSC, MRgFUS showed improvements in quality of life (QOL); this suggested that MRgFUS would be cost-effective in those patients with contraindications to DBS, or in those who refuse DBS for other reasons.

Overall, MSAC accepted that MRgFUS was cost-effective against the comparators. MSAC also considered it was important to consider patient preferences in this context; that is, weigh up AEs against the invasiveness of the procedure.

MSAC noted the estimated net impact to the MBS ranged from \$269,887 in Year 1 to \$302,700 in Year 6 (see Table 14). MSAC noted that the number of MBS claims for DBS, across all diagnoses (including Parkinson's disease), has been stable at approximately 250 per year since around 2011. The ADAR stated the number of claims used for ET would be 25% of the total claims. MSAC noted that the commentary disagreed with this proportion, suggesting this would be up to around 60%. However, MSAC noted the pre-MSAC response that 60% is unlikely based on patient numbers in Australia, and 25% was based on expert opinion. MSAC also noted that after listing MRgFUS, it is estimated that there will be a sudden increase in the number of claims as several patients will transfer from DBS; however, the pre-MSAC response argued that the financial impact of listing MRgFUS to the MBS would be less than \$500,000 per annum under all plausible scenarios including market growth rates due to MRgFUS of up to 140% because only a small number of patients would be eligible for treatment and the cost savings relative to DBS are substantial on a per patient basis. MSAC considered the net impact to the MBS may be marginally higher, if, in some patients, MRgFUS displaced DBS (rather than replaced). However, there was no data for this type of use (DBS after MRgFUS) in the studies included in the resubmission.

MSAC noted an implementation issue of equity of access, as MRgFUS is only available in two private hospitals in Sydney and Melbourne, requires expensive dedicated equipment and consumables, and requires trained and expert operators. MSAC also questioned given the limited number of sites at which MRgFUS is provided whether a non fee for service funding model for the procedure may be more appropriate.

MSAC noted the MRgFUS device uses a disposable single-use patient kit: Exablate Neuro Patient Accessory Kit (MRgFUS consumables). The Kit contains DQA gels, helmet sealant tubes, protective frame pin caps, long stereotactic frame pins and 3.0T silicone membranes or head coils with 1.5T silicone membranes, i.e. the Kit does not contain any invasive or implantable devices. The ADAR used the cost of the MRgFUS consumables of \$████ per patient, which was the price used in the determination of the cost-effectiveness of MRgFUS versus DBS. MSAC questioned who would pay these costs (private insurers, patients, or absorbed by the healthcare system). MSAC noted that Protheses List Advisory Committee (PLAC) previously rejected the application (Application N0025) to fund the Exablate Neuro Patient Accessory Kit on the PL as it did not meet the existing PL criteria (not implantable, not essential for implantation of or maintaining the prosthesis). Given this outcome, MSAC was concerned that there may be high

out of pocket costs associated with the service that may or may not be captured through private hospital insurance arrangements.

MSAC noted the pre-MSAC response, which the applicant considered that if the patient is privately insured then, even if the cost of consumables are not covered by the PL, these costs can be incorporated within the cost of hospitalisation which insurers will have an incentive to fund because MRgFUS is substantially less costly than DBS.

Overall, MSAC supported MBS listing of MRgFUS for the treatment of medically refractory ET, provided that a suitable set of item descriptors and fees can be agreed on and that attempts were made to address the funding of consumables. MSAC acknowledged the limitations in the clinical evidence, but accepted that MRgFUS addresses an unmet clinical need, has a different but acceptable safety profile, and has non-inferior effectiveness and acceptable cost-effectiveness compared with DBS. MSAC also considered it important that patients had the choice of a less-invasive procedure that had comparable safety and effectiveness to surgery. In addition, MSAC noted that MRgFUS was an accepted treatment alternative for refractory ET in other jurisdictions and had recently been accepted by the NHS in England⁵.

4. Background

This applicant developed assessment report (ADAR) is the first resubmission of [Application 1614](#).

At the March/April 2021 meeting, the Medical Services Advisory Committee (MSAC) did not support MBS listing of MRgFUS for the treatment of medically refractory ET. 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.

The resubmission provided a detailed summary of the MSAC concerns for the previous submission and how they have been addressed in the resubmission. This was summarised by the commentary in Table 1.

Table 1 Summary of key matters of concern

Component	Matter of concern	How the current assessment report addresses it (Assessment Group, i.e. commentary comments)
Population	MSAC considered whether the population could be limited to those who are considering using MRgFUS as an alternative to DBS.	Addressed. As noted in the PSD (p.4), this would be a difficult population to adequately define. The applicant agrees with MSAC and considers that restricting the proposed population to a group in which DBS is the alternative therapy is impractical, clinically inappropriate and likely to be unnecessary. No changes to the eligible population have been proposed in the resubmission.

⁵ NHS England, Clinical Commissioning Policy: Transcranial magnetic resonance guided focused ultrasound thalamotomy for treatment of medication-refractory essential tremor (adults) [200803P] (URN 1904), November 2020, available at <https://www.england.nhs.uk/wp-content/uploads/2020/11/1904-transcranial-magnetic-resonance-guided-focused-ultrasound-thalamotomy-for-treatment-of-medication-refract.pdf>

Component	Matter of concern	How the current assessment report addresses it (Assessment Group, i.e. commentary comments)
Clinical management algorithm	MSAC noted that the role of ipsilateral retreatment and contralateral (non-dominant) treatment was not supported by the current evidence base (PSD, p.1).	Addressed. Ipsilateral retreatment and contralateral treatment are excluded through the inclusion of a once per lifetime limit on the number of treatments per patient, as specified in the PICO Confirmation (Section A.2 and Section A.3).
Intervention	MSAC noted issues with the procedural requirements, fee structure and frequency of imaging (PSD, p.1) and suggested that a resubmission should have a packaged item rather than the six separate items within one application (PSD p.4).	Not adequately addressed. The applicant has attempted to simplify the fee structure by removing the item number and fee for the radiology component of the overall procedure, reducing the total number of proposed MBS items from 6 to 5. Further consideration may need to be given to the potential for the MRgFUS procedure to be further packaged, and the number of proposed MBS items decreased to account for the multi-staged process.
Intervention	The proposed MBS fee for pre-surgical planning with MRI remains higher compared to the ratified PICO.	Not adequately addressed. The resubmission states that the proposed MBS item wording and fee is based on two existing MBS items for planning of stereotactic neurosurgery (MBS item 63010) and stereotactic anatomical localisation for target verification (MBS item 40800). While this justification sounds reasonable, it may require further assessment by MSAC.
Proposal for public funding	The resubmission requested no limits be placed on speciality group delivering the intervention, as neurosurgeons, neurologists and radiologists may be able to perform the procedure, provided they were adequately trained and qualified (resubmission, p. 49).	Not adequately addressed. While expert advice suggests that the presence of both neurologist and neurosurgeon may be necessary, this may need further clarification in the wording of the MBS item.
Comparative effectiveness MRgFUS vs. DBS	MSAC noted that no [MCID] had been established for any of the tremor scales, despite PASC considering this to be critical. Statistically significant differences before and after treatment were found in studies, whether the differences were also clinically significant remains unknown. ESC considered that the resubmission's clinical claim of non-inferior effectiveness may be appropriate. 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 (no direct RCT), small numbers of patients, different methods of assessment of tremor severity, and in particular no MCID has been established and validated for ET. (PSD, ps.3 & 23)	MCID not adequately addressed in response. Assessment group provided a summary table for commentary detailing a distribution-based method for health-related quality of life (QUEST) and total tremor scores (CRST). The applicant provided an additional five studies and attempted to address the uncertainty surrounding the risk of bias assessments. Studies provided low-quality non-comparative evidence, but some concordance was provided regarding effectiveness for MRgFUS and DBS.

Component	Matter of concern	How the current assessment report addresses it (Assessment Group, i.e. commentary comments)
Comparative safety MRgFUS vs. DBS	MSAC also noted that MRgFUS creates an irreversible thalamic lesion, unlike DBS which is reversible. (PSD, p.3) MSAC considered that the claim that AEs are only short term with MRgFUS is uncertain, with limited long-term follow-up of MRgFUS (indirect treatment comparison follow-up of 12 months). Overall, MSAC agreed with ESC and considered that there is an uncertain safety profile. (PSD, p.3)	Addressed The applicant provided long-term follow-up data for both MRgFUS and DBS. However, the long-term data (up to 6-years) does not appear to refute MSAC concern about the applicant's claim that AEs for MRgFUS are short-term. While 5-year follow-up data for MRgFUS reported that most AEs had resolved or subsided, the MRgFUS adverse event 'ataxia' appears to have doubled.

Source: Table constructed during the evaluation based on Table 1, of resubmission, 1614 PSD and *Pre-ESC response*

MRgFUS = Magnetic Resonance guided Focused Ultrasound; MSAC = Medical Services Advisory Committee; PSD = Public Summary Document

5. Prerequisites to implementation of any funding advice

This was unchanged from the previous submission; refer to [PSD Application 1614, March-April 2021, pp4-5](#).

The details of staff training and other prerequisites such as quality assurance or licensing requirements were not discussed in the ADAR. However, an Insightec Exablate Neuro Training Plan was submitted by the applicant with the initial application documents. The training is limited to the safe and effective use of the device.

Equipment pre-requisites are a compatible MRI machine, a MRgFUS device (e.g., ExAblate® Neuro), and a disposable single-use patient kit. In Australia, the kit is registered with the MRgFUS system under the same listing on the Australian Register of Therapeutic Goods (ARTG).

The applicant lodged an application to the Prostheses List Advisory Committee (PLAC) for the Exablate Neuro Patient Accessory Kit (Application N002552) in January 2021. The applicant expects that this application will be reconsidered by PLAC once MRgFUS receives a positive recommendation by MSAC.

6. Proposal for public funding

MSAC previously requested the resubmission should have a packaged item as opposed to six separate items in one application. In the resubmission the applicant has removed one item, the radiology service from the ADAR, reducing the number of proposed items from six to five. The entire MRgFUS service now consists of two MRI items (before and after the procedure for pre- and post-treatment evaluation), and three items for performing the procedure itself.

The MBS item descriptors proposed in the ADAR are provided Tables 2, 3, 4, 5 and 6.

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

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> <p>Assessment of suitability for treatment of essential tremor with MRI-guided focused ultrasound</p> <p>Essential tremor where:</p> <p>(a) Symptoms cause severe disability, and</p> <p>(b) Tremor has proven refractory to, or recurred following, maximal medical therapy</p> <p>The service is not applicable to patients with a primary diagnosis of Parkinson’s disease^a</p> <p>Bulk bill incentive (Anaes.)</p>
<p>MBS Fee: \$403.20 Benefit: 75% = \$302.40 85% = \$342.75</p>

Source: First MBS listed item in Table 2, page 21 of the resubmission

a Note: 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

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>
<p>MBS Fee: \$994.60 Benefit: 75% = \$745.95 85% = \$845.41</p>

Source: Second MBS item listed in Table 2, page 21 of the resubmission

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

Category 3 – THERAPEUTIC PROCEDURES
<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> <p><i>Claimable only once per patient per lifetime.</i></p>
<p>MBS Fee: \$2,055.05 Benefit: 75% = \$1,541.29</p>

Source: Third MBS item listed in Table 2, page 21 of the resubmission

Bold italicised denotes the resubmission reinstating the restriction to limit MRgFUS to once per patient per lifetime (as requested by ESC)

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

Category 3 – THERAPEUTIC PROCEDURES
<p>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:</p> <p>Essential tremor where:</p> <p>(a) Symptoms cause severe disability, and</p> <p>(b) Tremor has proven refractory to, or recurred following, maximal medical therapy</p> <p>The service is not applicable to patients with a primary diagnosis of Parkinson's disease^a</p> <p>Multiple Operation Rule (Anaes.) (Assist.)</p> <p>Claimable only once per patient per lifetime</p>
<p>MBS Fee: \$3,165.50 Benefit: 75% = \$2,372.62</p>

Source: Fourth MBS item listed in Table 2, page 21 of the resubmission

a Note: Does not exclude patients with a primary diagnosis of ET with parkinsonian features consistent with the definition of ET plus **Bold italicised** denotes the resubmission reinstating the restriction to limit MRgFUS to once per patient per lifetime (as requested by ESC)

Table 6 Proposed MBS item descriptor – Post-surgical treatment assessment

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> <p>Assessment of treatment outcomes following MRI-guided focused ultrasound procedure</p> <p>Bulk bill incentive (Anaes.)</p> <p>Claimable only once per patient per procedure</p>
<p>MBS Fee: \$403.20 Benefit: 75% = \$302.40 85% = \$342.75</p>

Source: Fifth MBS item listed in Table 2, page 21 of the resubmission

The resubmission excluded the use of ipsilateral retreatment and contralateral treatment through reinstating the claimable only once per patients per lifetime for the intraoperative procedure (as requested previously by ESC; see red text in Tables 4 and 5).

The proposed MBS fee for pre-surgical planning with MRI remains higher compared to the ratified PICO (\$994.60 vs. \$336.00). The resubmission states that the proposed MBS item wording and fee is based on two existing MBS items for planning of stereotactic neurosurgery (MBS item 63010) and stereotactic anatomical localisation for target verification (MBS item 40800).

The resubmission requested no limits be placed on speciality group delivering the intervention, as neurosurgeons, neurologists and radiologists may be able to perform the procedure, provided they were adequately trained and qualified. The resubmission also stated that the intervention was currently performed by a neurosurgeon, but that other adequately trained physicians (neurologists or radiologists in particular) may also step in over time. The commentary noted that while expert advice suggests that the presence of both neurologist and neurosurgeon may be necessary, this may need clarification in the wording of the MBS item (i.e. number of specialists required).

The Department had offered to work with the applicant on revising items, but this did not occur before the resubmission. The Department continues to see a benefit in working directly with applicant to better determine number and descriptors of items and the associated fees from this.

7. Summary of public consultation feedback/consumer issues

Targeted consultation feedback was received from one (1) consumer, which was strongly supportive of the inclusion of MRgFUS on the MBS. Key benefits for the proposed intervention were identified as: allowing them to perform daily tasks they not previously able to, prior to treatment; able to return to main-stream employment, leading to improved social health; the procedure was non-invasive with a short recovery time (compared with DBS); improved quality of life and wellbeing of recipients ; allowing recipients to return to the labour force, reducing the need for pension and disability payments; and that there are no ongoing costs incurred with this treatment (once off payment). The only disadvantage identified by the consumer was its current cost.

For the summary of the consultation feedback from the previous submission refer to [PSD Application 1614, March-April 2021, p5.](#)

8. Proposed intervention's place in clinical management

This was unchanged from the previous submission; refer to [PSD Application 1614, March-April 2021, pp9-10.](#)

The resubmission stated that MRgFUS is positioned in line with Deep Brain Stimulation (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 DBS or remain on BSC.

9. Other options for MSAC consideration

N/A

10. Comparator

Unchanged from the previous submission, and consistent with the 1614 ratified PICO confirmation, the resubmission proposed unilateral or bilateral DBS as the main comparator for MRgFUS. BSC is proposed as a second comparator in those unwilling to accept the risks associated with DBS or are contraindicated for the procedure.

Unilateral DBS is currently covered by MBS items 40850, 40852, 40854, 40856, 40858, 40860 and 40862 while bilateral DBS is covered by MBS item 40851.

11. Comparative safety

Overview of evidence base

Evidence to inform the relative efficacy and safety of MRgFUS vs DBS comprised:

- two retrospective comparative studies (Level III evidence) - Huss et al. (2015)⁶ and Kim et al. (2017)⁷
- one systematic review and indirect treatment comparison (ITC) by Langford et al. 2018⁸ (Level III evidence) and
- a naïve comparison conducted with two non-comparative DBS studies and 14 non-comparative MRgFUS studies (Level IV evidence).

Of the 14 non-comparative MRgFUS studies, 5 were new to the resubmission – these comprised three prospective^{9,10,11}, and two retrospective^{12,13} studies.

Of the two non-comparative DBS studies, the resubmission considered one to have a low risk of bias and the other to have a moderate risk of bias. The resubmission noted that while the non-comparative MRgFUS studies were conducted in the USA, Europe and across Asia, the DBS studies included in the ITC and naïve comparison were largely limited to the USA suggesting that there may be some exchangeability issues.

In addition, the updated clinical evaluation presented the results of a recent systematic review by Giordano (2020)¹⁴ which includes a comparison of safety data from MRgFUS and DBS studies. The commentary noted that 6 studies' AE data from Giordano et al. (2020)⁹ was reported

⁶ Huss DS, Dallapiazza RF, Shah BB, Harrison MB, Diamond J, Elias WJ. Functional assessment and quality of life in essential tremor with bilateral or unilateral DBS and focused ultrasound thalamotomy. *Mov Disord*. 2015 Dec;30(14):1937-43.

⁷ Kim M, Jung NY, Park CK, Chang WS, Jung HH, Chang JW. Comparative Evaluation of Magnetic Resonance-Guided Focused Ultrasound Surgery for Essential Tremor. *Stereotact Funct Neurosurg*. 2017;95(4):279-286.

⁸ Langford BE, Ridley CJA, Beale RC, Caseby SCL, Marsh WJ, Richard L. 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 Health*. 2018 Oct;21(10):1168-1175.

⁹ Abe K, Horisawa S, Yamaguchi T, Hori H, Yamada K, Kondo K, Furukawa H, Kamada H, Kishima H, Oshino S, Mochizuki H, Kanemoto M, Hirabayashi H, Fukutome K, Ohnishi H, Igase K, Matsubara I, Ohnishi T, Sadamoto K, Taira T. Focused Ultrasound Thalamotomy for Refractory Essential Tremor: A Japanese Multicenter Single-Arm Study. *Neurosurgery*. 2021 Mar 15;88(4):751-757.

¹⁰ Jameel A, Gedroyc W, Nandi D, Jones B, Kirmi O, Molloy S, Tai Y, Charlesworth G, Bain P. Double lesion MRgFUS treatment of essential tremor targeting the thalamus and posterior sub-thalamic area: preliminary study with two year follow-up. *Br J Neurosurg*. 2021 Aug 12:1-10.

¹¹ Kim MJ, Park SH, Chang KW, Kim Y, Gao J, Kovalevsky M, Rachmilevitch I, Zadicario E, Chang WS, Jung HH, Chang JW. Technical and operative factors affecting magnetic resonance imaging-guided focused ultrasound thalamotomy for essential tremor: experience from 250 treatments. *J Neurosurg*. 2021 May 21:1-9..

¹² Fukutome K, Kuga Y, Ohnishi H, Hirabayashi H, Nakase H. What factors impact the clinical outcome of magnetic resonance imaging-guided focused ultrasound thalamotomy for essential tremor? *J Neurosurg*. 2020 May 1;134(5):1618-1623.

¹³ Wu P, Lin W, Li KH, Lai HC, Lee MT, Tsai KW, Chiu PY, Chang WC, Wei CY, Taira T. Focused Ultrasound Thalamotomy for the Treatment of Essential Tremor: A 2-Year Outcome Study of Chinese People. *Front Aging Neurosci*. 2021 Jul 14;13:697029.

¹⁴ Giordano M, Caccavella VM, Zaed I, Foglia Manzillo L, Montano N, Olivi A, Polli FM. Comparison between deep brain stimulation and magnetic resonance-guided focused ultrasound in the treatment of essential tremor: a systematic review and pooled analysis of functional outcomes. *J Neurol Neurosurg Psychiatry*. 2020 Dec;91(12):1270-1278.

separately; Elias et al. (2013)¹⁵, Elias et al. (2016)¹⁶, Huss et al. (2015)¹, Krishna et al. (2020)¹⁷, Sinai et al. (2019)¹⁸ and Wharen Jr et al. (2017)¹⁹.

A total of 15 studies were considered relevant to the evidence base for MRgFUS vs BSC. The pivotal evidence is a sham-controlled multicentre randomised controlled trial (RCT) (Level II evidence) by Elias et al. 2016¹¹ (Level II evidence) considered by the resubmission to have a low risk of bias. The 14 prospectively and retrospectively conducted non-comparative MRgFUS studies previously mentioned for MRgFUS vs DBS were included as supportive evidence to demonstrate consistency and durability of effect.

The resubmission also included more recent long-term follow-up data up to 5 years (Cosgrove 2021)²⁰ from the pivotal RCT.

The commentary identified an additional two non-comparative relevant DBS studies in the time period of the applicant literature search, i.e. to the 24 August 2021, and one recently published DBS study (published after the ADAR literature search) but concluded that the results of the additional two non-comparative studies do not impact the assessment of comparative safety and efficacy.

The commentary considered the overall quality of the evidence base to be low, and key studies were considered to be at high risk of bias including some that were rated as being of moderate risk of bias by the resubmission.

Adverse events

MRgFUS vs DBS

While AEs related to MRgFUS are relatively frequent, they are either mild or (less frequently) moderate in severity and transient, with most events resolving within 12 months.

The most common intraprocedural AEs for MRgFUS included dizziness, headache, nausea, and heat sensation, and tended to be limited to the procedure duration (up to a maximum of 3 months post-treatment). AEs related to the placement of the stereotactic frame (pain, scalp injuries from the stereotactic frame pins) were also reported. No intraprocedural AEs were reported for the DBS.

Post-procedural AEs related to MRgFUS most frequently included paraesthesias and gait disturbances and tended to be either transient or improve with time. AEs related to DBS included balance or gait difficulties and speech disturbances, some resolving after hardware

¹⁵ Elias WJ, Huss D, Voss T, Loomba J, Khaled M, Zadicario E, Frysinger RC, Sperling SA, Wylie S, Monteith SJ, Druzgal J, Shah BB, Harrison M, Wintermark M. A pilot study of focused ultrasound thalamotomy for essential tremor. *N Engl J Med.* 2013 Aug 15;369(7):640-8.

¹⁶ Elias WJ, Lipsman N, Ondo WG, Ghanouni P, Kim YG, Lee W, Schwartz M, Hynynen K, Lozano AM, Shah BB, Huss D, Dallapiazza RF, Gwinn R, Witt J, Ro S, Eisenberg HM, Fishman PS, Gandhi D, Halpern CH, Chuang R, Butts Pauly K, Tierney TS, Hayes MT, Cosgrove GR, Yamaguchi T, Abe K, Taira T, Chang JW. A Randomized Trial of Focused Ultrasound Thalamotomy for Essential Tremor. *N Engl J Med.* 2016 Aug 25;375(8):730-9.

¹⁷ Krishna V, Sammartino F, Cosgrove R, Ghanouni P, Schwartz M, Gwinn R, Eisenberg H, Fishman P, Chang JW, Taira T, Kaplitt M, Rezai A, Rumià J, Gedroyc W, Igase K, Kishima H, Yamada K, Ohnishi H, Halpern C. Predictors of Outcomes After Focused Ultrasound Thalamotomy. *Neurosurgery.* 2020 Aug 1;87(2):229-237.

¹⁸ Sinai A, Nassar M, Eran A, Constantinescu M, Zaaroor M, Sprecher E, Schlesinger I. Magnetic resonance-guided focused ultrasound thalamotomy for essential tremor: a 5-year single-center experience. *J Neurosurg.* 2019 Jul 5:1-8.

¹⁹ Wharen RE Jr, Okun MS, Guthrie BL, Uitti RJ, Larson P, Foote K, Walker H, Marshall FJ, Schwab J, Ford B, Jankovic J, Simpson R, Dashtipour K, Phibbs F, Neimat JS, Stewart RM, Peichel D, Pahwa R, Ostrem JL; SJM DBS ET Study Group. Thalamic DBS with a constant-current device in essential tremor: A controlled clinical trial. *Parkinsonism Relat Disord.* 2017 Jul;40:18-26.

²⁰ Cosgrove, G. R. (2021). Magnetic Resonance Guided Focused Ultrasound Thalamotomy For Essential Tremor – Long Term Follow-Up Results. Not published

programming. Additionally, wound infections at the implant site and other complications related to the DBS hardware were reported, some requiring hardware replacement over time. Longer-term AEs for DBS at 4-6.5 years post-procedure reported long-term neurological issues (e.g. paresthesia, hand ataxia, dysarthria, gait disturbance, dystonia) in 26-37% of patients.

The resubmission also presented evidence for the long-term safety of DBS. The resubmission concluded that DBS is associated with a range of long-term safety issues, that are unlikely to be less significant than those associated with MRgFUS (primarily paraesthesia of low to moderate severity).

The resubmission stated that the results from Giordano (2020)⁹ showed that the overall the overall complication rate was similar between MRgFUS and DBS, the distribution of complications was significantly different among the two groups. The MRgFUS group had a higher prevalence of gait disturbances/muscle problems ($p < 0.001$), paraesthesia ($p < 0.001$) and nausea ($p < 0.001$), while the DBS group had a higher prevalence of speech disturbances ($p < 0.001$) and local adverse symptoms ($p < 0.001$). Note that the analysis of “all” DBS procedures presented in Table 7 includes unilateral DBS and bilateral DBS. The rate of complications specifically associated with bilateral procedures would be expected to be higher.

Table 7 Prevalence of complications for MRgFUS and DBS (Giordano, 2020)

Complication	MRgFUS	DBS	
		Unilateral	All
N	477	247	731
gait disturbance	164 (34.4%)	30 (12.1%)	80 (10.9%)
Paresthesias/numbness	175 (36.7%)	35 (14.2%)	64 (8.8%)
Speech disturbance	26 (5.5%)	16 (6.5%)	81 (11.1%)
Lead problems	0 (0%)	36 (14.6%)	83 (11.4%)
Infection	0 (0%)	2 (0.8%)	13 (1.8%)
Intracranial haemorrhage	0 (0%)	3 (1.2%)	8 (1.1%)
Seizures	0 (0%)	1 (0.4%)	4 (0.5%)
Oedema/haematoma	0 (0%)	0 (0%)	1 (0.1%)
Local adverse symptoms	26 (5.5%)	36 (14.6%)	80 (10.9%)
Nausea	29 (6.1%)	4 (1.6%)	4 (0.5%)
Mental deficits	0 (0%)	15 (6.1%)	37 (5.1%)
Other	64 (13.4%)	23 (9.3%)	61 (8.3%)
Death	0 (0%)	1 (0.4%)	1 (0.1%)
Total complications	484	202	517

Source: Giordano (2020)

Overall the resubmission claimed that for MRgFUS vs DBS, the safety was “different, yet non-inferior”. However the commentary concluded that there is uncertainty around this claim based on the following concerns: (1) the identified comparative evidence was very limited, (2) existing evidence base was found to be at a high risk of bias, and (3) the two procedures have a different safety profile, particularly in terms of transient adverse events (AEs, e.g. no intraprocedural sensations for DBS as inserted under general anaesthesia, potential hardware-related complications for DBS, irreversibility of MRgFUS vs fully-reversible DBS). The safety profile of the two procedures is different so a meaningful comparison of adverse events as reported in the evidence base is difficult to carry out. The commentary therefore argued that the clinical claim for safety for MRgFUS vs DBS may need to be revised to “somewhat uncertain”.

In response to the commentary's conclusions about the uncertainty of the evidence on safety the applicant argued that:

- limitations of the comparative evidence were addressed in the resubmission by including the best practice matched adjusted indirect comparison (MAIC) and updated naïve comparison between MRgFUS and DBS
- MRgFUS having a "different" AE profile to DBS does not mean it has a worse AE profile and having both MRgFUS and DBS funded on the MBS would allow patients the option to choose the AE and risk-profile that is most suitable for their circumstances and well-being.
- The claim of serious risk of bias in studies cited is inconsistent with other health technology assessments (HTAs) including the OHTAS model cited by ESC in response to the previous submission.

MRgFUS vs BSC

AEs related to MRgFUS were similar to those reported in MRgFUS vs DBS. Some AEs (intraprocedural or post-procedural) were experienced by 50/56 (91%) of patients who received MRgFUS. Of note, 12/20 (60%) of patients who received a sham procedure also reported procedure-related AEs. Longer-term data to 6 years follow-up for MRgFUS reported that most AEs had resolved (e.g. unsteadiness, dysarthria, taste disturbances and fatigue) or subsided (e.g. paraesthesia, imbalance, and muscle weakness). However, the 5 year Elias et al. (2016)¹¹ data reported in the unpublished Cosgrove (2021)¹⁵ manuscript noted the MRgFUS rate of ataxia had doubled from 1.3% at 3 years to 2.6% at 5 years.

The resubmission concluded that although MRgFUS is considered to have an inferior safety profile relative to BSC, the evidence demonstrates the procedure to be safe and well tolerated.

Overall the commentary concluded that the data presented does not provide sufficient additional evidence to refute the MSAC concern regarding the claim of short-term AEs for MRgFUS. Clarification was sought from the applicant on the implications of the finding on ataxia. In response the applicant noted that the doubling of the rate of ataxia referred to in Cosgrove (2021)¹⁵ is due to one additional patient with ataxia and the study investigators did not consider this additional case to be related to the procedure. The applicant reiterated that overall the 5-year data it cited support the conclusion that AEs associated with the MRgFUS procedure continue to resolve over time.

12. Comparative effectiveness

MRgFUS vs DBS

Both MRgFUS and DBS achieved statistically significant improvements from baseline to the last follow-up in total tremor (CRST total, percentage change from baseline, range, 32.5-78.3% for MRgFUS and 22.5-84.2% for DBS); hand tremor (range, 39.8-80% for MRgFUS and 44.8-78.9% for DBS); tremor-related disability (Part C of the CRST, range 38-85.4% 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). The commentary noted that the pooled results of the MRgFUS non-comparative studies should therefore read 72.5% (range, 56.5-78.9%; k=7 studies) at 3 months and 68.9% (range, 42.4-80%; k=11 studies) at 12 months post-treatment.

The commentary concluded that the existing evidence base for MRgFUS vs DBS was at high risk of bias with limited comparative evidence exists. However 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 six years of follow-up for DBS and 5 years for MRgFUS) and the evidence suggests that the clinical effectiveness of MRgFUS is similar to DBS. Across both MRgFUS and DBS overall motor, activities of daily living (ADL) and hand function scores were also durable over the longer-term.

No minimum clinically important difference (MCID) threshold has been determined for essential tremor. The commentary completed a MCID for QUEST and CRST (quality of life and tremor scales respectively) using a distribution-based method and determined that MRgFUS compared to Sham met the 0.5 standard deviation MCID threshold and appeared to demonstrate a MCID. They were unable to complete one against DBS. The commentary concluded that the evidence available does not allow for unequivocal conclusions regarding the clinical effectiveness of MRgFUS compared to 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						

Outcomes (units) Follow-up	Participants (studies)	Quality of evidence (GRADE)	Reduction with MrgFUS	Reduction with DBS	Mean difference	Comments
Total CRST, 12 months	MRgFUS=208; k=8 DBS=215; k=2	⊕⊕⊕⊕	56.5%	55.1%	2.4%	No significant difference
CRST Part C, 12 months	MRgFUS=269; k=7 DBS=97; k=1	⊕⊕⊕⊕	68.2%	71.4%	9.3%	No significant difference

Source: Table 3 of resubmission

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)

MRgFUS vs BSC

Relative to BSC, MRgFUS significantly reduced total tremor, hand tremor, tremor-related disability and quality of life. While improvements tended to diminish with time, significant improvements compared to baseline were reported for up to five years post-procedure.

The table summarising the balance of clinical benefits and harms from key studies was unchanged from the previous submission; refer to [PSD Application 1614, March-April 2021, p. 15, Table 9](#).

Clinical claim

On the basis of the benefits and harms reported in the evidence base, the resubmission proposes that, relative to DBS, MRgFUS has a different yet non-inferior safety and non-inferior effectiveness.

The commentary concluded that while the clinical claim presented in the resubmission might be reasonable, uncertainties exist around whether the safety of MRgFUS relative to DBS should be considered non-inferior or somewhat uncertain.

On the basis of the benefits and harms reported in the evidence base, the resubmission proposes that, relative to BSC, MRgFUS has inferior safety and superior effectiveness.

The commentary concluded that the claim for MRgFUS vs BSC presented in the resubmission is reasonable but noted that the quality of evidence is moderate for MRgFUS vs BSC due to concerns about the methodological quality (high risk of bias).

Translation issues

The resubmission's summary of modelling inputs and assumptions derived in Section C pre-modelling studies are summarised in Table 9.

Table 9 Summary of translation issues

Model Parameter	Base case model input		Source/Justification
	MRgFUS	DBS	
Treatment effect			
Short-term efficacy of MRgFUS and DBS	Health state occupancy post-treatment with MRgFUS or DBS procedures for ET: <ul style="list-style-type: none"> • 53% will experience marked improvement in ET • 47% will experience mild or moderate improvement in ET 		Section C.2 Based on the assumptions in the OHTAS model
Rates of recurrence in MRgFUS and DBS patients	Rates of recurrence are equal between MRgFUS and DBS <ul style="list-style-type: none"> • Year 1 = 8.9% • Year 2 – 5 = 1.36% 		Section C.2 Section D model applies conservative assumption of equal rates of recurrence based on MRgFUS RCT data.
Rates of reoperation in patients that experience a tremor recurrence	40%		Section C.2 Based on assumptions in OHTAS model.
Short-term treatment-related adverse events – resolve in first year post-treatment			
Short-term adverse event rates in MRgFUS and DBS patients (resolve in first year)	Dysarthria/dysphagia 5.5% Paraesthesia 18.6% Gait disturbance 20.9% Headache 5.5% Lead fracture 0.0% Nausea/vomiting 6.1% Mental state change/deficits 0.0% Other 10.6%	Dysarthria/dysphagia 6.2% intracerebral hematoma/haemorrhage 1.1% Paraesthesia 6.6% Gait disturbance 9.1% Headache 8.3% Infection 1.8% Lead fracture 11.4% Nausea/vomiting 0.5% Mental state change/deficits 3.6% Seizures 0.5% Oedema 0.1% Other 7.1%	Section C.3 Table 74 Based on the Transient AE rates reported in Giordano et al. (2020) .
Transformation of short-term adverse event rates to QALYS	QALY loss due to STAE = 0.0277	QALY loss due to STAE = 0.0209	Section C.3 Table 77 Utility estimates and duration of AE reported in OHTAS model (primary) and Ravikumar et al. (2017) model (where OHATS model did not report utility estimates) are applied to AE

Model Parameter	Base case model input		Source/Justification
	MRgFUS	DBS	
			rates reported in Giordano et al. (2020) .
Transformation of short-term adverse event rates to HCRU costs	Cost of STAE = \$56.41	Cost of STAE = \$2,066.32	Section C.3 Table 79 Australian MBS cost estimates are applied to AE rates reported in Giordano et al. (2020) .
Long term treatment-related adverse events			
Long-term adverse event rates in MRgFUS and DBS patients	Paraesthesia 18.1% Gait disturbance 13.5% Other 2.8%	Paraesthesia 2.2% Gait disturbance 1.8% Dysarthria/dysphagia 4.9% Headache 2.6% Other 1.2% Mental state change 1.5%	Section C.3 Table 75 Giordano et al. (2020)
Transformation of long-term adverse event rates to health state utilities	Utility value in patients with LTAE that have: • Marked improvement: 0.65 • Mild/moderate improvement: 0.74 Based on 81.4% LTAE utility multiplier	Utility value in patients with LTAE that have: • Marked improvement: 0.60 • Mild/moderate improvement: 0.69 Based on 75.6% LTAE utility multiplier	Section C.3 Table 78 Weighted average of LTAE and HS utility values published in OHTAS model and Ravikumar et al. (2017) model where OHTAS model does not provide utility inputs.

AE, adverse events; DBS, deep brain stimulation; HS, health state; LTAS, long term adverse event; MRgFUS, Magnetic Resonance-guided Focused Ultrasound; OHTAS, Ottawa Health Technology Assessment Series; QALY, quality adjusted life year; STAE, short term adverse event

Source: Table 57, pp101-102 of the commentary (based on Table 80 of the resubmission, pp201-202)

13. Economic evaluation

The economic evaluation is summarised in Table 10.

Table 10 Summary of the economic evaluation

Perspective	Health care system
Comparator	Deep brain stimulation
Therapeutic claim: effectiveness	Non-inferior effectiveness
Therapeutic claim: safety	Different, yet non-inferior safety profile
Type of economic evaluation	Cost-utility analysis
Sources of evidence	Elias et al. (2016), Huss et al. (2015), Halpern et al. (2019), Giordano et al. (2020)
Time horizon	5 years
Outcomes	Markov model
Health states	Marked Improved tremor: Post-primary surgery Mild Improved tremor: Post-primary surgery Tremor recurrence: Reoperation Marked Improved tremor: Post reoperation Mild Improved tremor: Post reoperation Tremor recurrence: No reoperation Dead
Cycle length	Annual
Discount rate	5%
Software packages used	TreeAge

Source: Table 87, p 207 of the resubmission 1614.1

The resubmission presented the structure of the model as a Markov model with a cycle length of 1 year, as patients are usually monitored annually for disease progression.

All patients entered the model with disabling tremor, and patients could progress with a marked improvement, or a mild-moderate improvement, and with or without long term adverse events. These patients then progress through the model taking into consideration: survival, recurrence, reoperation, battery replacement (for DBS), and either marked or mild improvement. This structure has been adopted from the validated OHTAS model. The commentary concluded that it was economically valid, and most likely clinically valid.

The commentary noted that it would have been more informative to have a model which stratifies adverse events as health states to determine the direct impact of adverse events in the model given MSAC's previous statements that a meaningful comparison between DBS and MRgFUS was difficult due to the different safety profiles and uncertain claim of comparative effectiveness. However due to the numerous adverse events included in the model, the commentary observed that it was not practical to include every adverse event as an individual health state.

In the model, adverse events are calculated by determining the utility value of adverse events as reported in the OHTAS model, and if not reported in the OHTAS report, as reported by Ravikumar et al. (2017).²¹ The proportion of adverse events as reported by Giordano et al. (2020)⁹ are then applied to the utility values to get a weighted average which is applied within each health state. An AE multiplier is applied to patients with longer term adverse events, calculated from the proportion of permanent (12 month) adverse events as reported by Giordano et al. (2020)⁹, multiplied by the utility values of each adverse event, and presented as a weighted average of these values.

The resubmission presented a stepped evaluation, firstly replicating the OHTAS model, then adapting the model to include more Australian specific assumptions (Table 11). The stepped analysis shows an incremental difference of 0.08 QALYS over 5 years (discounted) in favour of

²¹ 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.

DBS in the resubmission base case compared to 0.25 QALYs in favour of DBS in the OHTAS model.

The stepped analysis shows that the difference in QALY between the original OHTAS model and the resubmission base case is primarily driven by the assumption of 0% recurrence in DBS vs MRgFUS patients. Relaxing this assumption and allowing DBS patients to recur at the same rate as MRgFUS patients (consistent with a clinical claim of non-inferior effectiveness) removes one third of the incremental QALYs estimated for DBS in the OHTAS model (0.24 to 0.16).

Table 11 Stepped evaluation of the impact of difference in modelling assumption on Incremental QALY between OHTAS and submission model

Model parameter	OHTAS base case	Submission base case	Incremental QALYs (MRgFUS vs. DBS)
OHTAS model base case			-0.25
Discounting	1.5%	5%	-0.24
Lifetables (+Discounting)	Canadian lifetables	Australian life tables	-0.24
Rates of recurrence (+Lifetables and Discounting)	<u>MRgFUS</u> Year 1 = 8.9% Year 2-5 = 4.7% <u>DBS</u> 0%	<u>MRgFUS</u> Year 1 = 8.9% Year 2-5 = 1.36% <u>DBS</u> Year 1 = 8.9% Year 2-5 = 1.36%	-0.16
Short term AE profile and utility estimates (+Rates of recurrence, Lifetables and Discounting)	QALY loss due to STAE: <u>MRgFUS</u> = 0.0419 <u>DBS</u> = 0.0021	QALY loss due to STAE: <u>MRgFUS</u> = 0.0277 <u>DBS</u> = 0.0209	-0.12
Long-term AE profile and utility estimates (+Long-term AE profile and utility estimates, Rates of recurrence, Lifetables and Discounting)	Proportion of patients with LTAE: MRgFUS = 23% DBS = 0% Long-term adverse event utility multiplier: MRgFUS = 0.814 DBS = not applicable	Proportion of patients with LTAE: MRgFUS = 34% DBS = 14% Long-term adverse event utility multiplier: MRgFUS = 0.814 DBS = 0.756	-0.08 (resubmission base case)

Source: Table 104 p232 MSAC 1614.1 resubmission

AE, adverse event; OHTAS, Ontario Health Technology Assessment Series; QALY, quality adjusted life year; MRgFUS, Magnetic Resonance-Guided Focused Ultrasound; DBS, Deep Brain Stimulation; LTAE, long term adverse event

The economic model employs the following conservative assumptions in favour of DBS:

- There may be mortality advantages with MRgFUS over DBS (based on ICH risks with DBS observed in Sobstyl 2019) which are not incorporated in the CUA approach. The OHTAS model, and this resubmission, assumes an intracranial haemorrhage with DBS will be completely resolved within one month.
- A DBS battery life of 4 years was applied to all patients with non-rechargeable generators. Evidence suggests the battery life of newer generation devices may be 3 years.
- Capital costs associated with MRgFUS were likely overestimated because they are based on a throughput of █ procedures per year which is lower than the █ that were performed by the one active system at St Vincent's Hospital in 2019, increasing applied capital costs from \$█ to \$█
- Medical service costs associated with MRgFUS were also likely overestimated. It was conservatively assumed the three MBS items for the intraoperative procedure would be accrued by three separate physicians. In practice, it is expected that over time the service will be performed by two physicians meaning the multiple operation rule will apply for at least a proportion of MRgFUS cases.

- There are circumstances other than waning of treatment effect that could lead to a complete loss of treatment effect due device malfunction in patients treated with DBS which require removal and replacement of the device. While the model accounts for rates of these AE leading to device replacement, no disutility is applied for loss of treatment effect and as such these events are not counted as a “recurrence” in the model.
- The base case model assumes that 34% and 14% of MRgFUS and DBS patients respectively experience persistent long-term adverse events (LTAEs) based on Giordano (2020)⁹. However, the only comparative evidence of DBS and MRgFUS in ET patients, Huss (2015)¹, reported that 20% and 24% of MRgFUS and DBS patients respectively experience persistent LTAE. Under these circumstances there would be a net incremental QALY benefit in favor of MRgFUS (se univariate sensitivity analysis).
- The systematic review by Giordano (2020)⁹ found an average percentage improvement in terms of quality of life which was statistically significantly in favour of MRgFUS; 61.9% (SD: ±7.9) for MRgFUS vs 52.5% (SD: ±16.2) for DBS group. Whereas the model assumes that health state utility values are the same in either treatment arm. However, a higher level of quality of life in patients treated with MRgFUS would likely result in a net incremental QALY gain in favour of MRgFUS.

The resubmission presents the results of the base case economic model results (Table 12). MRgFUS is less costly than DBS but also has less benefit, as the ICER is in the southwest quadrant of the cost-effectiveness plane (Figure 1). The resubmission provides an inverse argument, that with the ICER being in the southwest quadrant, for every additional QALY gain for DBS compared with MRgFUS, the cost is \$383,877, and as this ICER is significantly higher than traditional cost-effectiveness thresholds considered reasonable for MSAC, MRgFUS should be considered cost-effective compared with DBS. The commentary noted that the justification that DBS is not cost-effective compared with MRgFUS is contentious but potentially valid as there is precedent to support this counterfactual approach.

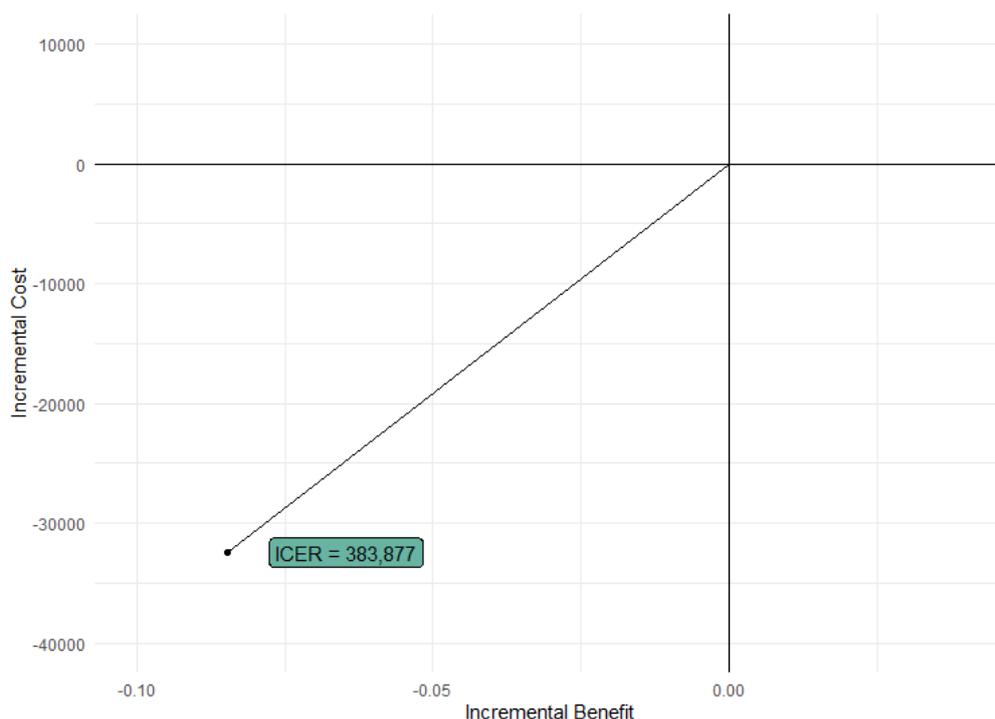
Table 12 Incremental cost effectiveness ratio for MRgFUS compared with DBS

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
MRgFUS	\$44,866	-\$32,467	3.6308	-0.0846 ^a	\$383,877
DBS	\$77,333		3.7154		

ICER = Incremental Cost Effectiveness Ratio; QALY, quality adjusted life year

^a 13% of the QoL gains sourced from transient adverse events.

Figure 1 Cost effectiveness plan showing base case incremental costs and benefits as described in the resubmission



Source: Figure 1 of the commentary

One of the main sources of uncertainty of the resubmission model is the calculation of transient and persistent adverse events. The resubmission demonstrated that increasing the transient AE disutility in the MRgFUS arm, while decreasing the proportion of patients with persistent adverse events results in a lower incremental cost between the two interventions, but also a lower incremental benefit, resulting in a higher ICER (\$529,325/QALY gained – see Table 13).

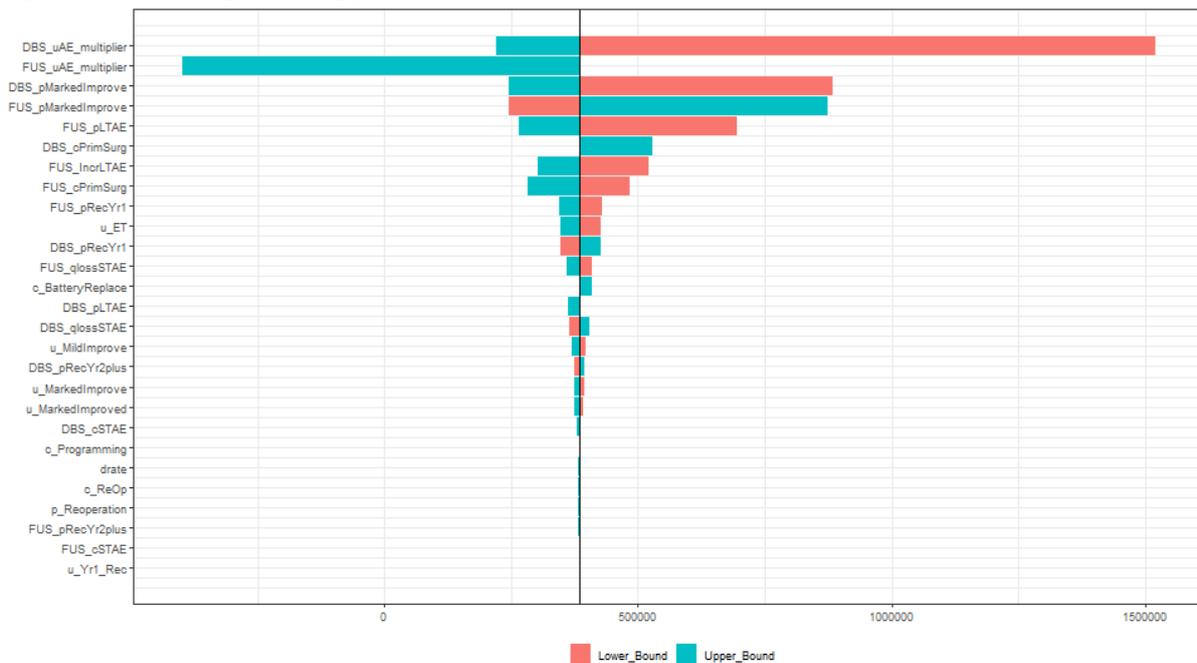
Table 13 Sensitivity analyses regarding AE profile inputs into the economic model

Model Parameter	Giordano 2020 AE rates (base case)		Huss 2015 AE rates (sensitivity)	
	MRgFUS	DBS	MRgFUS	DBS
Transient AE costs	\$56.41	\$2,067.44	\$300.54	\$535.56
Transient AE disutility	0.0277	0.0209	0.1463	0.0264
Proportion of patients with Persistent AE	34%	14%	20%	24%
Persistent AE health state utility multiplier	0.8143	0.7561	0.8100	0.7683
Incremental costs	-\$32,467		-\$30,674.36	
Incremental QALYs	-0.0846		-0.0579	
ICER	\$383,877		\$529,325.50	

Source: Table 108 of resubmission

The commentary further tested each parameter of the model for key drivers by changing each parameter by 20%. In doing so, the utility adverse event multiplier for each treatment was found to be the key drivers of the model, followed by the transition probability for marked improvement for each arm, and the probability of long-term adverse events for MRgFUS. As such, the utility multiplier is the most important variable in the model to determine the validity of the model and how reflective the model is in quantifying value. Additionally, the incremental cost of MRgFUS is always less than DBS (when varying parameters by ±20%), with the exception of increasing the AE multiplier for MRgFUS by +20%.

Figure 2 Tornado diagram of key parameters

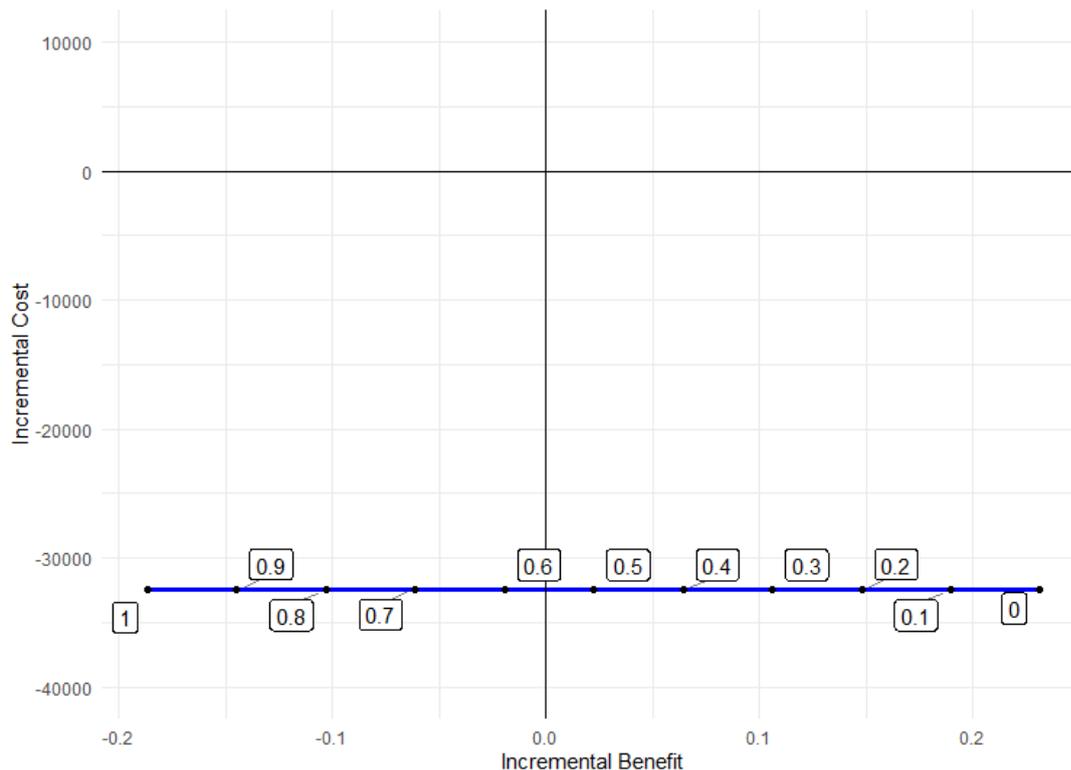


Source: Figure 2 of the commentary

Of note, the applicant disagreed with the claim that the multiplier was a key driver of the model, noting that when this variable is completely removed, the results of the model remained in the south-west quadrant of the cost effectiveness plane. Instead the applicant argued that the main driver of the results of the cost-utility analysis is the conservatively estimated cost saving of greater than \$30,000 per patient in favour of MRgFUS (as outlined in Table 105 of the resubmission).

A threshold analysis was conducted by the assessment group to assess what the impact of any variation in the utility multiplier had to the model. By varying the utility multiplier for MRgFUS from 0 to 1 in 10% increments, the ICER changed from \$35,518/QALY gained (multiplier = 0), through to \$328,469/QALY gained when the multiplier was set at 0.80. When the multiplier is set to near 0.90, the accrued benefit for MRgFUS is greater than the accrued benefit for DBS, resulting in a dominant ICER for MRgFUS (Figure 3).

Figure 3 Threshold analysis changing the utility adverse event multiplier for DBS



Source: Figure 3 of the commentary

By varying the utility multiplier for DBS from 0 to 1 in 10% increments, the impact to the ICER is reversed, changed from dominance (multiplier = 0), becoming a positive value ICER when the DBS utility multiplier parameter was set to ~0.55. The ICER decreases from \$1,679,694/QALY gained when the DBS utility multiplier parameter is set at 0.6 to \$173,964/QALY gained, when the DBS utility multiplier parameter is set at 1.0.

It is unlikely that the MRgFUS utility multiplier parameter would be greater than 0.90 and unlikely that the DBS utility multiplier parameter would be less than 0.55, therefore MRgFUS would not be dominant over DBS.

The commentary noted that there are discrepancies between the Giordano et al. (2020)⁹ and the Ravikumar et al. (2017)¹⁶ systematic reviews in identifying transient adverse events, suggesting the totality of the different adverse event profiles of the two interventions are not adequately quantified. The resubmission's sensitivity analysis in Table 13 which uses the adverse event profile from the Huss et al (2015)¹ study also attempted to address this uncertainty. With this sensitivity analysis, there is less cost savings with MRgFUS compared with DBS (\$30,674: Huss et al 2015¹; compared with \$32,467: base case) but also less incremental difference in benefit favouring DBS (-0.0579: Huss et al 2015¹; compared with -0.0846: base case). The resubmission uses this analysis to justify the base case as the conservative estimate. However the commentary noted that the use of the Huss et al (2015)¹ adverse events means the resubmission also sources more utility values from Ravikumar et al (2017)¹⁶, which increases the uncertainty of these results.

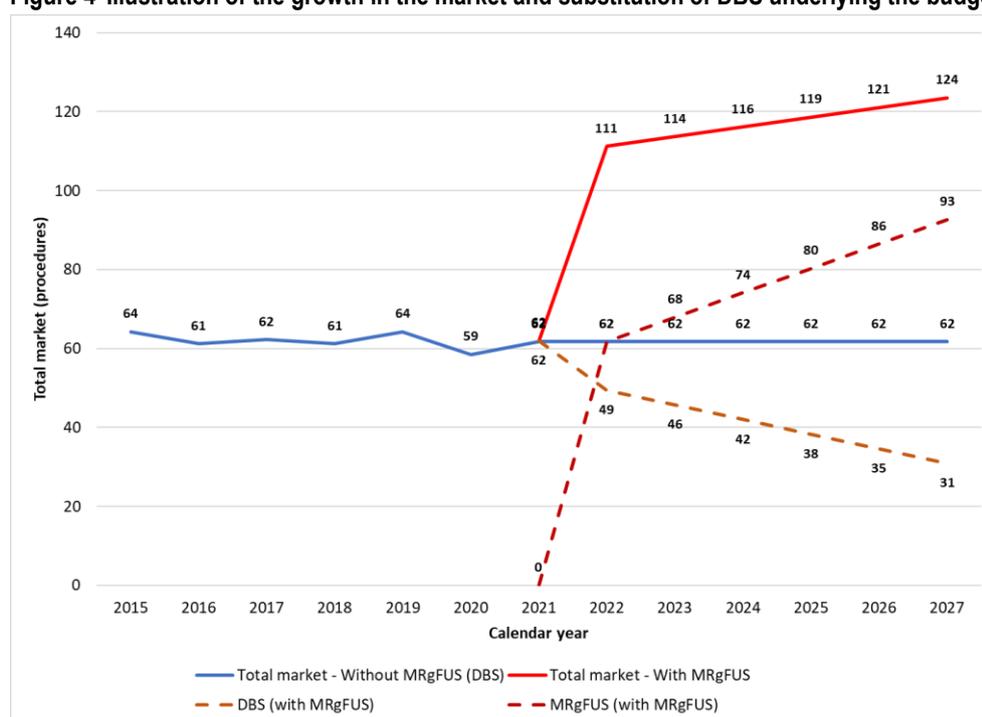
The applicant's pre-ESC response noted that both Giordano et al. (2020)⁹ and Ravikumar et al. (2017)¹⁶ were based largely on level IV evidence; however, as Ravikumar did not report long term AEs and because ESC have previously considered Ravikumar (2017)¹⁶, it was considered appropriate to include estimates from Giordano (2020)⁹ in the base case.

14. Financial/budgetary impacts

The financial analysis assumed proportions of otherwise privately-funded MRgFUS patients and otherwise ET-specific DBS patients would transition to MBS-funded MRgFUS. This was in response to MSAC comments on the previous submission that there could be a large demand for this treatment from people who would prefer to not undergo DBS given a choice. To account for this the resubmission incorporates growth in the market, over and above the growth due to current caseload outside the MBS. It is assumed additional market growth will be 80% in year 1. The caseload projections are illustrated in Figure 4. A mixed-methods approach using multiple sources of data was used to estimate MBS-funded MRgFUS patients. The new model omits the 1 to 3 patients per year included in utilisation estimates for retreatment that were in the previous submission.

Existing and projected MBS-funded ET-specific DBS procedures were estimated using a combination of MBS, Australian Institute for Health and Welfare (AIHW) and Australian Prudential Regulation Authority (APRA) data. Existing MRgFUS use shifting to an MBS setting was estimated as a function of procedure numbers in the two Australian centres where MRgFUS is currently available, St Vincent's Hospital Sydney and FMIG, Melbourne. A percentage of these MRgFUS services occurring in a world without MBS reimbursement were expected to shift to an MBS treatment setting post MBS listing. APRA data was used to estimate the proportion of ET hospitalisations occurring in an MBS treatment setting, assuming the proportion of ET patients with private health insurance is the same as the general population. The commentary noted that the assumption that private health insurance rates are the same among ET patients as among the general population is not based on evidence.

Figure 4 Illustration of the growth in the market and substitution of DBS underlying the budget impact analysis



Source: Figure 36, p 243 of the resubmission

The commentary concluded that the resubmission appropriately identified patient populations on active treatment that may switch to MBS listed MRgFUS and the methodological approach for identifying these patients was generally appropriate. However, it was noted that the resubmission did not explicitly consider potential utilisation from ET patients otherwise on sub-optimal pharmacological treatments and/or BSC.

The financial implications to the MBS resulting from the proposed listing of MRgFUS are summarised in Table 14. The commentary concluded that while the forecasts estimated in the

resubmission are likely to be overestimated due to increased uptake rates, the resubmission underestimates the proportion of DBS patients who have ET. The resubmission identified Australian ET hospitalisation data (from AIHW) and used these parameters to determine the proportion of the MBS items for DBS which would be used for ET patients. At the same time, the resubmission assumes any overnight hospitalisation for ET would be for DBS, though arriving ultimately at an assumption that 25% of MBS services for DBT patients would be attributable to ET. However, using this logic consistently, the proportion of DBS patients with ET should be 61.7%.

The italicised text denotes updated financial estimates using updated estimates based on the assumption that 61.7% of all current DBS services are for essential tremor based on the logic outlined above. This increased proportion is different from the estimated proportion of ET patients provided in the initial application and PICO confirmation (25%). The commentary concluded that there is potential for the net cost/year to the MBS to be greater than in the resubmission, however less than estimated in the resubmission for the overall health care system (including private health insurance).

Table 14 Net financial impact of MRgFUS to the total health care system

Row	Healthcare budget	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
A	Net impact to the MBS (\$)	\$269,887 \$666,082	\$277,653 \$685,248	\$284,797 \$702,878	\$290,150 \$716,090	\$295,699 \$729,785	\$302,700 \$747,063
B	Net impact to private insurers - hospital costs (\$)						
C	Net impact to private insurers - prosthesis costs (\$)						
D	Net impact to health care system – expenditure (\$)						
E	Net impact to health care system - patients treated	49 122	52 128	54 134	57 140	59 146	62 152

Source: Table 123 p253 resubmission 1614.1

MBS, Medicare Benefits Schedule; MRgFUS, Magnetic Resonance-Guided Focused Ultrasound

15. Key issues from ESC to MSAC

ESC key issue	ESC advice to MSAC
Uncertainties with the item descriptors	<p>There are several concerns for the resubmission's proposed MBS multi-item descriptors:</p> <ul style="list-style-type: none"> • Whether the two MRI items (before [#1] and after [#5] the procedure for pre- and post-treatment evaluation should be funded • Whether the fee for the MRI for pre-surgical planning (#2) was sufficiently justified given non-invasive procedure • The relative roles of clinicians performing the complete service remain unclear [#3 and #4] and require further clarification, especially given that the model of care has been based on DBS <p>To note the Department is still considering the composition of the MBS package and will continue to work with applicant on the wording and fees of the item descriptor.</p>
Safety	Despite the limited comparative evidence, there was consistency in the results suggesting safety for MRgFUS is sustained up to 5 years.
Effectiveness	Uncertainty remains regarding clinical effectiveness as there is still no established MCID for tremor scores and there is no randomised controlled study compared to DBS, however improvement in tremor scales are similar to DBS.
Uncertainties regarding the long-term adverse event 'multiplier' and how QALYs are modelled	The method used to model long-term adverse events does not appear to be conceptually appropriate. However, it may be sufficient to enable general exploration and establish a broad range of plausible ICERs to inform MSAC's considerations. MSAC should consider that any improvements in the model will be subject to limitations in the evidence to inform the model inputs.
Interpretation of the ICER	The interpretation of the "fewer quality-adjusted life years (QALYs), lower cost" (southwest ICER quadrant) outcome should consider that the modelled QALY loss is small, consistent with the effectiveness and safety claims, cost savings are likely to be substantial and, importantly, the intervention presents an opportunity for patients to align their treatment with preferences regarding invasiveness and safety profile.
Risk of high OOP cost to the consumer	The MRgFUS consumables are currently unsuitable for funding on the PL as it did not meet the PL criteria for listing given the PL is not intended to cover consumable products.
Financial impacts	The financial impacts are uncertain within a defined range and identified list of factors. The impact on public hospital admissions is unclear.

ESC discussion

ESC noted that this application was a resubmission for a Medicare Benefits Schedule (MBS) listing of MRI-guided focused ultrasound (MRgFUS) to treat medically refractory essential tremor (ET). ESC noted that in 2021, MSAC accepted that there was an unmet clinical need for a non-invasive intervention compared with MBS-funded deep brain stimulation (DBS), but did not support the application because of the evidence for comparative safety (including that adverse events for MRgFUS were only short-term) was too uncertain and – as a consequence – the economic evaluation was inappropriate. In addition, 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. MSAC also suggested that a resubmission should have a packaged item rather than the six separate items within one application.

ESC noted that the applicant has agreed to one treatment per lifetime, thereby excluding the use of ipsilateral retreatment and contralateral treatment.

ESC noted the applicant has attempted to simplify the fee structure by removing the item number and fee for the radiology component of the overall procedure, reducing the total number of proposed MBS items from 6 to 5. ESC noted several issues for the proposed MBS items:

- #1 MRI for pre-surgical suitability (see Table 2): ESC queried whether this item should be funded given that it may or may not lead to treatment. ESC also noted the lack of a once per lifetime restriction for this proposed item, which may lead to the risk of inappropriate multiple claims
- #2 MRI for pre-surgical planning (see Table 3): ESC queried whether the fee amount was justified given it was based on a neurosurgical planning item and further explanation is requested.
- Treatment/interoperative procedure by the neurologist (#3; see Table 4); and by the neurosurgeon (#4; see Table 5): ESC noted the relative roles of clinicians performing the complete service are unclear, especially given that the model of care has been based on DBS. ESC also noted that a neurologist/neurosurgeon is necessary but that this is not justified in the proposed fees. In addition, ESC considered that guidance on appropriate qualification or training is needed and clarity on which specialists are required (noting that the DBS item numbers do not specify the specialists). Post-ESC, the Department reiterated that confusion remained because of the uncertain training requirements for the item and this required some further clarification either in the item descriptor or explanatory notes so that billing issues could also be resolved.
- #5 MRI for post-surgical treatment assessment (see Table 6): ESC noted this item is to assess patient outcomes and exclude potential complications but queried whether this item was necessary and how it would lead to a change in management. Post-ESC, the Department considered that this assessment service could be considered a form of aftercare and therefore potentially included in the main procedure.

ESC noted that the Department is still considering the number of MBS items and the composition of the MBS package, noting the pre-ESC response, where the applicant cited earlier advice it received from the Department that packaging the item numbers could be difficult to implement due to the fact that it is a multi-staged and multi-disciplinary process. ESC noted the Department's current proposal for a two-item structure:

- Item 1: pre-surgical suitability assessment which is a service that may be conducted at any diagnostic imaging site with the appropriate imaging capabilities and expertise
- Item 2: which captures all other requirements of the complete service (including intraoperative and assessment of treatment outcomes) which is likely to be conducted exclusively at the two sites listed in the application who currently provide this service. As noted above, the Department considered that post-surgical assessment could be considered a form of aftercare and therefore part of the main procedure captured in this item.

Post-ESC, the Department clarified that this two-item structure would need to recognise the additional complexity and training required for the pre-surgical assessments under the new item 1 and a once per lifetime restriction would still be required for both items.

ESC noted that, at MSAC's previous consideration of this application in 2021, MSAC considered whether it would be possible to limit this population to those who are considering using MRgFUS as an alternative to DBS. However, it was agreed that this would be a difficult population to adequately define.

ESC noted that the comparators in the resubmission were unchanged: DBS as the main comparator, and best supportive care as a secondary comparator (relevant to the subgroup of the proposed population contraindicated or unsuitable for surgery).

ESC noted that there is limited new comparative evidence included in the resubmission and the updated evidence base was largely low quality: five new single-arm studies for MRgFUS, one systematic review comparing safety data for MRgFUS and DBS (Giordano 2020) which was stated to provide a more comprehensive review of comparative safety data than provided in the indirect treatment comparison (ITC) by Langford (2018) (limited to studies that met specific assessment criteria), and one unpublished follow-up report (Cosgrove 2021) of the pivotal sham-controlled multicentre randomised controlled trial (RCT) trial reporting to 5 years follow-up. ESC noted the pre-ESC response considered that it is ethically unfeasible to conduct a DBS-controlled randomised controlled study due to explicit patient preference for MRgFUS (risk of attrition bias) and the fact that the patient characteristics differ and vary in terms of inclusion criteria.

In terms of comparative safety of MRgFUS vs DBS, ESC noted that results were largely unchanged showing that intra-procedural adverse events (AEs) were common with MRgFUS vs no intra-procedural sensations with DBS; no serious AEs for MRgFUS vs serious AEs from potential hardware-related complications with DBS; and post procedural AEs 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. ESC considered the recent meta-analysis results from Giordano (2020) showing that the overall complication rate was similar but distribution of adverse events was significantly different among the two groups; MRgFUS had higher prevalence of paraesthesia/numbness, gait disturbance and nausea but lower prevalence of speech disturbance and local adverse events (relative to DBS). ESC considered that the uncertainty with comparative safety still remains, because the safety profiles are different – there are different adverse effects between DBS (invasive, reversible) and MRgFUS (non-invasive/permanent). ESC noted that the commentary considered that the clinical claim of a different yet non-inferior safety profile remained to be uncertain mainly due to the limited comparative evidence provided in the resubmission and existing evidence base was at high risk of bias. The pre-ESC response considered the bias assessment was significantly overstated, noting that it was inconsistent with other health technology assessments (HTAs) such as the Ontario HTA of MRgFUS done in 2018.

In terms of comparative effectiveness of MRgFUS vs DBS, ESC noted that the results were largely unchanged, 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 also noted that the issue regarding the minimum clinically important difference (MCID) has not (and cannot) be resolved as it has not been established for any of the tremor scales. This does not allow for unequivocal conclusions regarding the clinical effectiveness of MRgFUS and DBS. Overall, ESC considered that improvement in tremor scales are similar to DBS and that the clinical claim of non-inferior efficacy was reasonable.

ESC considered the secondary comparison of MRgFUS vs best supportive care (BSC), noting that the results were unchanged showing that MRgFUS had a higher proportion of patients who experienced procedure-related adverse events when compared with sham. ESC noted that the failed procedure rate was 5/56 (9%). ESC also considered that the unpublished 5 year follow-up results from the pivotal RCT showed that adverse events for MRgFUS remained stable or improve over time. ESC noted the commentary's concern for long term-safety of MRgFUS mainly related to the doubling of the rate of ataxia, which the pre-ESC response clarified was informed from only one additional patient. ESC considered that the clinical claim of inferior safety and superior effectiveness was reasonable.

Overall, ESC considered that there were no significant changes in conclusions for safety and effectiveness in light of updated evidence. ESC noted there was consistency in the results from low quality evidence suggesting that longer term safety was sustained for up to five years.

ESC noted that the availability and quality of evidence and input data were key limitations of the economic evaluation.

ESC noted that the resubmission addressed the previous MSAC concern regarding comparative safety by including a cost-utility analysis comparing MRgFUS vs DBS. The resubmission used a Markov model that was based on the published Ontario Health Technology Assessment Series (OHTAS) model, which was referred to in the Public Summary Document (PSD) Application 1614, March-April 2021. The other published CUA model referred to in the PSD was by Ravikummar (2017), which ESC recalled had a high level of uncertainty in the transformation of adverse events to quality-adjusted life years (QALYs). ESC noted that most utilities were sourced from the OHTAS model. However, ESC considered there was limited justification for why the OHTAS model was selected as a basis for the economic evaluation.

ESC noted the model structure was simplistic but replicated from the OHTAS model and adapted to the Australian setting. ESC considered the Markov traces for both model arms, noting limited health state transitions over time and similarities between model arms. ESC also noted that the model relied on parameter assumptions (e.g. rates of recurrence assumed to be the same between model arms) including assumptions carried over from the OHTAS model (e.g. short term efficacy rate of MRgFUS and DBS; and rate of reoperation if recurrence was assumed to be the same between model arms) but considered that the assumptions were generally reasonably justified considering limited data to inform the model. ESC noted the commentary's proposal that it would have been more informative for the model to stratify adverse events as health states, but it was unclear how this could be implemented in practice considering limited available evidence regarding numerous adverse events to be included in the model. ESC considered the 5-year timeframe of the model was appropriate, but that there may be opportunity in the future to extend this due to emerging (albeit weak) evidence.

ESC considered the most significant issue with the resubmission's model was the quantification of adverse events and the impact these events have in the model. ESC considered it unclear why the long-term adverse event "multiplier" (the base case used a multiplier of 0.814 for MRgFUS and 0.756 for DBS) was used instead of a standardised weighted utility or applying additional disutility. ESC also queried the behaviour of the long-term adverse event multiplier in the base case model, noting that it did not produce credible values under stress testing (e.g. such as setting all AE rates set to 0 or to 100%). ESC noted the commentary's threshold analysis but considered it was unclear why testing would be performed over the value range 0-1 and queried if an alternative range of values may be appropriate for this parameter. Overall, ESC considered that the method used to model long-term adverse events did not appear to be conceptually appropriate. However, ESC recognised that opportunities for further improving the model may be limited, and considered that the model presented in the resubmission might be sufficient to enable general exploration and establishing a broad range of plausible ICERs to inform MSAC's considerations. ESC queried whether the multiplier was a limitation of the OHTAS model approach adopted. The assessment group clarified it was not and that the presented approach was independently developed by the resubmission.

ESC noted that the interpretation of the "fewer QALYs, lower cost" (southwest ICER quadrant) outcome should consider that the modelled QALY loss is small, consistent with the "different but non-inferior" safety profile and non-inferior effectiveness claim; cost savings are likely to be substantial; and, importantly, the intervention presents an opportunity for patients to align their treatment with preferences regarding invasiveness and safety profile.

ESC noted that the resubmission's model had a number of transparency and quality issues and ideally more work could be done for its consideration by MSAC. However, ESC also considered that further refinements of the model may not contribute enough additional understanding to substantially progress decision-making, and that any attempts at improving the model will be subject to limitations in the evidence that is required to inform its structure and inputs.

ESC noted the method and data sources to estimate the financial estimates were unchanged in the resubmission. ESC noted that market growth was accounted for, assumed at 80% in Year 1, equivalent to all current cases being conducted outside the MBS shifting to the MBS, which could be an overestimate. ESC noted retreatment with MRgFUS was appropriately not included in the financial estimates. ESC also noted that the commentary revised the financial estimates (see

Table 14) taking into account that all current DBS procedures are performed in private setting, i.e. assuming no DBS procedures in public hospital setting. ESC noted the pre-ESC response suggesting there is little data available to inform how patients are managed through the public hospital system. However, as noted in the commentary, a greater increase in utilisation results in a higher cost to the MBS but also a higher cost savings to the overall healthcare system.

ESC queried how the consumables included in the procedure will be funded. ESC noted that the single-use patient kit necessary for the procedure was rejected for inclusion on the Prostheses List (PL). Application N002552 was found to be unsuitable as it did not meet the PL criteria for listing given the PL is not intended to cover consumable products. ESC queried whether this could change in the future, as the PL is currently under review. ESC noted that the Department queried whether the cost of the consumable should be added to the procedural fee or if it has already been captured in the descriptor. Post-ESC, the Department reiterated that if the patient kit could not be listed on the PL the applicant would still need to resolve the question of the source of its funding.

ESC noted that the intervention is currently available in two private centres in Australia (St Vincent's Hospital, Sydney, and the Future Medical Imaging Group Centre, Melbourne) and that there would be significant equity of access issues. In the private setting, the intervention is currently self-funded by patients. ESC considered the small volume of services undertaken in private centres and whether additional service centres were overall a more efficient means of meeting demand than facilitating travel to one of the existing centres.

ESC noted there was no new consumer feedback for the resubmission. ESC discussed consumer issues such as: the uncertainty and risk of high out-of-pocket costs to the consumer, the fact consumers may prefer MRgFUS because it is less invasive than DBS, and uncertainty around whether a radiologist or a neurosurgeon is required to perform the procedure.

16. Applicant comments on MSAC's Public Summary Document

The applicant, Insightec, welcomes MSAC's support for the MBS listing MRgFUS in the treatment of medically refractory essential tremor. We thank the clinicians and patients who helped in achieving this recommendation.

As alluded to by MSAC, we will work directly with the Department of Health to determine the most efficient and equitable item descriptors and associated fees so that MRgFUS can be included on the MBS for the benefit of patients without unnecessary delay.

17. Further information on MSAC

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