Australian Government

Department of Health

# Application Form

## Magnetic Resonance-Guided Focused Ultrasound (MRgFUS) for the Treatment of Medically Refractory Essential Tremor (ET)

**(New Request for Public Funding)**

# PART 1 – APPLICANT DETAILS

**1. Applicant details (primary and alternative contacts)**

| |
|---|
| Corporation / partnership details (where relevant): Not applicable |
| Corporation name: Insightec Ltd |
| ABN: N/A |
| Business trading name: Insightec Ltd |

**Primary contact name:** REDACTED

| |
|---|
| Primary contact numbers |
| Business: REDACTED |
| Mobile: REDACTED |
| Email: REDACTED |

**Alternative contact name:** REDACTED

| |
|---|
| Alternative contact numbers |
| Business: REDACTED |
| Mobile: REDACTED |
| Email: REDACTED |

**2. (a) Are you a lobbyist acting on behalf of an Applicant?**

☒ Yes (REDACTED)
☐ No

**(b) If yes, are you listed on the Register of Lobbyists?**

☒ Yes
☐ No

# PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

**3. Application title**

Magnetic Resonance-Guided Focussed Ultrasound (MRgFUS) for the treatment of Medically Refractory Essential Tremor (ET)

**4. Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)**

ET is a chronic, progressive neurological condition characterised by rhythmic and oscillatory tremors of the upper extremities, not attributable to another cause (e.g. Parkinson's disease). With a prevalence of ~4% in adults ≥ 40 years (Louis 2010), ET is one of the most common neurological disorders among adults. With a poorly understood pathophysiology, ET is heterogeneous in its clinical presentation, pharmacological response profile and disease progression (Louis 2014).

Depending on disease severity, ET can lead to significant functional and social impairment. For moderate to severe ET, pharmacological interventions may provide symptomatic relief, although complete tremor-control is rare (Hedera 2013). It is estimated that 30-50% of patients are completely resistant to first line pharmacological therapy, with drug tolerance occurring in a further 13% of patients after chronic treatment (Koller 1989; Zesiewicz 2011). For these medically refractory patients, surgical interventions e.g. deep brain stimulation (DBS) are currently the only effective treatment options.

**5. Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)**

MRgFUS is a non-invasive, one-step method of targeted tissue thermal ablation used to treat medically refractory ET. The procedure combines focused ultrasound (FUS) and magnetic resonance imaging (MRI) to ablate the ventralis intermediate nucleus (VIM) of the thalamus. The heat from MRgFUS causes a small lesion on the targeted spot on the thalamus, interrupting the abnormal activity associated with ET. The use of MRI permits precise localisation, ablation, and real-time monitoring of the targeted tissue to prevent collateral damage to adjacent healthy tissue (Quadri et al., 2018; Abe & Taira, 2017). The delivery of the thermal ablation is done through an intact skull without the need for incision or craniotomy.

The creation of highly accurate and controllable lesions through MRgFUS leads to immediate clinical results. The lack of requirement for insertion of invasive probes means there is a minimal risk of bleeding and no risk of infection (Fishman 2018).

**6. (a) Is this a request for MBS funding?**

☒ Yes
☐ No

**(b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?**

☐ Amendment to existing MBS item(s)
☒ New MBS item(s)

This MSAC application is seeking new MBS items so that MRgFUS is reimbursed for medically refractory ET. However, it should be noted that item(s) already existing on the MBS could be used or amended to accommodate this procedure.

In particular, Recommendation 23 of the Draft Report from the Neurosurgery and Neurology Clinical Committee (2018) for the MBS Review Taskforce recommended MBS item 40801 be sufficiently broad so as to "ensure the MBS remains fit for purpose as technological approaches to deep brain lesioning progress". The Committee made particular note of focused ultrasound in tremor and noted item 40801 "would cover

use in tremors in most cases". https://www1.health.gov.au/internet/main/publishing.nsf/Content/mbs-review-2018-taskforce-reports-cp/$File/Neurosurgery-and-Neurology-Clinical-Committee.docx

Should Recommendation 23 be implemented, then there may not be a need for a complete MSAC Assessment of MRgFUS. However, should this application progress to a full MSAC assessment (and MRgFUS is recommended for funding) then implementation of funding could potentially be accommodated by amending 40801, based on clear advice that 40801 is appropriate for MRgFUS without any amendments or by addition of a new item to the MBS.

New MBS items for the neurology and radiology components of the service will likely be required. See PART 8 for more information.

**(c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service:**

N/A

**(d) If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?**

i. ☐ An amendment to the way the service is clinically delivered under the existing item(s)
ii. ☐ An amendment to the patient population under the existing item(s)
iii. ☐ An amendment to the schedule fee of the existing item(s)
iv. ☐ An amendment to the time and complexity of an existing item(s)
v. ☐ Access to an existing item(s) by a different health practitioner group
vi. ☐ Minor amendments to the item descriptor that does not affect how the service is delivered
vii. ☐ An amendment to an existing specific single consultation item
viii. ☐ An amendment to an existing global consultation item(s)
ix. ☐ Other (please describe below):

N/A

**(e) If a new item(s) is being requested, what is the nature of the change to the MBS being sought?**

i. ☐ A new item which also seeks to allow access to the MBS for a specific health practitioner group
ii. ☒ A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)
iii. ☐ A new item for a specific single consultation item
iv. ☐ A new item for a global consultation item(s)

**(f) Is the proposed service seeking public funding other than the MBS?**

☒ Yes
☐ No

**(g) If yes, please advise:**

N/A

**7. What is the type of service:**

- [x] Therapeutic medical service
- [ ] Investigative medical service
- [ ] Single consultation medical service
- [ ] Global consultation medical service
- [ ] Allied health service
- [ ] Co-dependent technology
- [ ] Hybrid health technology

**8. For investigative services, advise the specific purpose of performing the service *(which could be one or more of the following)*:**

N/A

i. [ ] To be used as a screening tool in asymptomatic populations
ii. [ ] Assists in establishing a diagnosis in symptomatic patients
iii. [ ] Provides information about prognosis
iv. [ ] Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
v. [ ] Monitors a patient over time to assess treatment response and guide subsequent treatment decisions

**9. Does your service rely on another medical product to achieve or to enhance its intended effect?**

- [ ] Pharmaceutical / Biological
- [x] Prosthesis or **device**
- [ ] No

A disposable patient kit (described in question 12) is required for MRgFUS to achieve its intended effect. Whilst this kit is disposable and not a prosthesis as such. It will require a funding stream and could potentially be included in Part C of the prosthesis list.

**10. (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?**

N/A

- [ ] Yes
- [ ] No

**(b) If yes, please list the relevant PBS item code(s):**

N/A

**(c) If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?**

N/A

- [ ] Yes (please provide PBAC submission item number below)
- [ ] No

**(d) If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?**

N/A

**11. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List?**

☐ Yes
☒ No

An application for the disposable patient kit to be included on the Prosthesis List (Part C) will be made as this assessment progresses through the MSAC process.

**(b) If yes, please provide the following information (where relevant):**

Billing code(s): Insert billing code(s) here
Trade name of prostheses: Insert trade name here
Clinical name of prostheses: Insert clinical name here
Other device components delivered as part of the service: Insert description of device components here

**(c) If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)?**

☐ Yes
☒ No

**(d) Are there any other sponsor(s) and / or manufacturer(s) that have a similar prosthesis or device component in the Australian market place which this application is relevant to?**

☐ Yes
☒ No

**(e) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):**

Insert sponsor and/or manufacturer name(s) here

**12. Please identify any single and / or multi-use consumables delivered as part of the service?**

Single use consumables:
Critical to the procedure is a disposable patient kit comprising:

- DQA gel: Tissue mimicking phantom gel used for Daily Quality Assurance (DQA).
- Helmet sealing tube: Water-tight coupling to the transducer.
- Cleaning kits: Set of products used for cleaning the system after each treatment.
- Protective frame pin caps: Silicone protective caps used to cover the frame pins for membrane protection.
- Stereotactic frame pins: Used for stereotactic frame fixation
- Silicone membranes: For coupling of patient head to focussed ultrasound helmet with/without an imaging enhancement coil

# PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

**13. (a) If the proposed medical service involves the use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer or any other type of therapeutic good, please provide the following details:**

Type of therapeutic good: Hyperthermia system, ultrasound
Manufacturer's name: Insightec Ltd
Sponsor's name: Insightec Ltd

**(b) Is the medical device classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?**

☐ Class III
☐ AIMD
☒ No

**14. (a) Is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?**

☐ Yes (If yes, please provide supporting documentation as an attachment to this application form)
☒ No

**(b) If no, has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?**

☒ Yes (if yes, please provide details below)
☐ No

ARTG listing, registration or inclusion number: ARTG: 260438 and 128137
TGA approved indication(s), if applicable: Malignant or benign tumours, or other disease conditions
TGA approved purpose(s), if applicable: To produce and control the delivery of high heat, i.e. temperatures greater than 43 degrees Celsius, to the body for the treatment of malignant or benign tumours, or other disease conditions. It is capable of producing whole body or localized heating effects within tissue or organs using an ultrasonic energy source.

**15. If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA?**

N/A

☐ Yes (please provide details below)
☐ No

**16. If the therapeutic good is not in the process of being considered for listing, registration or inclusion by the TGA, is an application to the TGA being prepared?**

N/A

☐ Yes (please provide details below)
☐ No

# PART 4 – SUMMARY OF EVIDENCE

***17.*** **Provide an overview of all key journal articles or research published in the public domain related to the proposed service that is for your application (limiting these to the English language only).** ***Please do not attach full text articles, this is just intended to be a summary.***

| | Type of study design* | Title of journal article or research project (including any trial identifier or study lead if relevant) | Short description of research (max 50 words)** | Website link to journal article or research (if available) | Date of publication*** |
|---|---|---|---|---|---|
| **Randomised controlled trial and OLE** | | | | | |
| 1. | International, multicentre, RCT of MRgFUS vs Sham control | A Randomized Trial of Focused Ultrasound Thalamotomy for Essential Tremor<br>Elias 2016.<br>ET-002; NCT01827904 | Patients diagnosed with medically refractory ET were randomised to receive MRgFUS (N=56) or Sham procedure (N=20) and followed over a 12-month period.<br>Significant reduction in tremor scores (CRST) and disability (CRST part C) as well as significant improvements in HRQoL and ADL (QUEST) were observed with MRgFUS compared with no change among patients receiving sham. | https://www.nejm.org/doi/full/10.1056/NEJMoa1600159 | August 25, 2016 |
| | | A Prospective Trial of Magnetic Resonance–Guided Focused Ultrasound Thalamotomy for Essential Tremor: Results at the 2-Year Follow-up.<br>Chang 2018<br>ET-002; NCT01827904 | Two years follow up of RCT ET-002 (Elias 2016).<br>Significant improvements in tremor and disability scores were observed from baseline at 6 months post procedure and maintained at one and two year follow up. | https://onlinelibrary.wiley.com/doi/abs/10.1002/ana.25126 | December 19, 2017 |

| | Type of study design* | Title of journal article or research project (including any trial identifier or study lead if relevant) | Short description of research (max 50 words)** | Website link to journal article or research (if available) | Date of publication*** |
|---|---|---|---|---|---|
| | | Four-Year Follow-Up Results of Magnetic Resonance-Guided Focused Ultrasound Thalamotomy for Essential Tremor<br>Park et al., 2019<br>ET-002; NCT01827904 | Subgroup of RCT patients (N=15) treated with MRgFUS at the investigation site in Korea with follow up data at 4 years.<br>The study demonstrates sustained improvements in tremor and disability scores over 4 years. No permanent adverse events were observed and no newly developed events occurred during 4 years of follow up. | https://onlinelibrary.wiley.com/doi/abs/10.1002/mds.27637 | February 13, 2019 |
| **Prospective single arm studies** | | | | | |
| | Prospective, single arm, single centre study over 5 years | Magnetic resonance–guided focused ultrasound thalamotomy for essential tremor: a 5-year single-center experience<br>Sinai 2019 | Fourty four patients treated with unilateral MRgFUS ventral intermediate nucleus (VIM) thalamotomy were assessed using the Clinical Rating Scale for Tremor (CRST) score and the Quality of Life in Essential Tremor Questionnaire (QUEST) over a 5-year period. Significant improvements in tremor, disability and QoL scores were observed and maintained up to 5 years. AEs were mild and occurred within a week of procedure and reversible in all but 5 patients (11%). | https://www.ncbi.nlm.nih.gov/pubmed/31277064 | July, 2019 |

| | Type of study design* | Title of journal article or research project (including any trial identifier or study lead if relevant) | Short description of research (max 50 words)** | Website link to journal article or research (if available) | Date of publication*** |
|---|---|---|---|---|---|
| | Open-label, uncontrolled, single arm single centre study | A pilot study of focused ultrasound thalamotomy for essential tremor<br>Elias 2013 | Unilateral MRgFUS used in 15 patients with severe, medication-refractory ET. Thermal ablation of the thalamic target occurred in all patients. Significant improvements observed in tremor, disability and QoL. Adverse effects of the procedure included transient sensory, cerebellar, motor, and speech abnormalities, with persistent paresthesias in four patients. | https://www.nejm.org/doi/full/10.1056/NEJMoa1300962 | August 15, 2013 |
| | Prospective single centre, single arm study | Magnetic resonance guided focused ultrasound thalamotomy for tremor: a report of 30 Parkinson's disease and essential tremor cases<br>Zaaroor 2018 | Patients with severe medication-resistant tremor underwent unilateral VIM thalamotomy using MRgFUS. Effects on tremor were evaluated using CRST in 18 patients with ET. SIgnfiiant imporemtns were observed in both CRST and QUEST scores. Adverse events were transient and none lasted beyond 3 months. | https://www.ncbi.nlm.nih.gov/pubmed/28298022 | January, 2018 |
| **Safety studies** | | | | | |
| 2. | Pooled Safety analysis of five cohorts | Neurological Adverse Event Profile of Magnetic Resonance Imaging–Guided Focused Ultrasound Thalamotomy for Essential Tremor<br>Fishman 2018 | Analysis of safety data for MRgFUS (N=186, five studies) to determine the safety profile of unilateral treatment for ET, including frequency, and severity of adverse events, including serious adverse events. Procedure-related SAEs were infrequent (1.6%), without intracerebral hemorrhages or infections. AEs were usually transient and commonly rated as mild (79%) and rarely severe (1%). | https://onlinelibrary.wiley.com/doi/abs/10.1002/mds.27401 | April 27, 2018 |

| | Type of study design* | Title of journal article or research project (including any trial identifier or study lead if relevant) | Short description of research (max 50 words)** | Website link to journal article or research (if available) | Date of publication*** |
|---|---|---|---|---|---|
| **Systematic literature reviews and meta-analyses** | | | | | |
| 3. | Systematic literature review and meta-analysis | A meta-analysis of outcomes and complications of magnetic resonance–guided focused ultrasound in the treatment of essential tremor<br>Mohammed 2018 | Systematic review and meta analysis conducted to analyze the overall outcomes and complications of MRgFUS in the treatment of essential tremor (ET). The MA comprised 1 RCT, 6 retrospective and 2 prospective studies. | https://thejns.org/focus/view/journals/neurosurg-focus/44/2/article-pE4.xml | February, 2018 |
| **Comparative studies** | | | | | |
| 5. | Indirect comparison of MRgFUS vs other interventions for ET | Focused ultrasound Thalamotomy and Other Interventions for Medication-Refractory Essential Tremor: An Indirect Comparison of Short-Term Impact on Health-Related Quality of Life<br>Langford 2018 | A systematic literature review was conducted to identify clinical, health-related quality of life (HRQoL), and economic evidence for each intervention. The matching-adjusted indirect comparison and simulated treatment comparison results demonstrated no evidence of a difference in efficacy (CRST) and HRQoL (CRST Part C) outcomes between MRgFUS and unilateral DBS in the short term (≤12 months) | https://www.ncbi.nlm.nih.gov/pubmed/30314617 | October, 2018 |
| 6. | Retrospective chart review, single centre | Functional assessment and quality of life in essential tremor with bilateral or unilateral DBS and focused ultrasound thalamotomy<br>Huss 2015 | A retrospective study of medication-refractory essential tremor patients with bilateral Vim DBS (n = 57), unilateral Vim DBS (n = 13), or unilateral focused ultrasound Vim thalamotomy (n = 15). Tremor was rated for all patients before and after treatment, using the Clinical Rating Scale for Tremor and Quality of Life in Essential Tremor Questionnaire. | https://onlinelibrary.wiley.com/doi/abs/10.1002/mds.26455 | December, 2015 |

| | Type of study design* | Title of journal article or research project (including any trial identifier or study lead if relevant) | Short description of research (max 50 words)** | Website link to journal article or research (if available) | Date of publication*** |
|---|---|---|---|---|---|
| **Health technology assessments** | | | | | |
| 7. | Cost effectiveness analysis of MRgFUS vs other interventions for treatment of ET | Magnetic Resonance-Guided Focused Ultrasound Neurosurgery for Essential Tremor: A Health Technology Assessment.<br>Health Quality Ontario 2018. | Systematic review of MRgFUS neurosurgery alone or compared with other interventions for the treatment of moderate to severe, medication-refractory ET. Markov cohort models were created to assess the cost-effectiveness of MRgFUS neurosurgery compared with other treatment options, including no surgery. | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5963668/ | May 3, 2018 |
| **Horizon Scanning** | | | | | |
| 8. | Technology Brief Update | Technology Brief Update: MR-Guided Focused Ultrasound (MRgFUS)<br>Health Technology Reference Group | Technology Brief Update on MR-Guided Focused Ultrasound (MRgFUS). The Health Technology Reference Group undertakes horizon scanning of new and emerging technologies. The review concludes that for the treatment of neurological disorders, MRgFUS "*may be a safe and effective treatment in comparison to invasive deep brain stimulation (DBS)*".<br>However, this review is not a comprehensive HTA. It is envisaged the MSAC evaluation and assessment process will supersede any advice provide of this brief update. | Not published online | June 2019 |

** Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*
***Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes.*
**** If the publication is a follow-up to an initial publication, please advise.*

**18. Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only). *Please do not attach full text articles, this is just intended to be a summary.***

| | Type of study design* | Title of research (including any trial identifier if relevant) | Short description of research (max 50 words)** | Website link to research (if available) | Date*** |
|---|---|---|---|---|---|
| 1. | International, multicentre, RCT of MRgFUS vs Sham control | Three-Year Follow-Up of Prospective Trial Of Focused Ultrasound Thalamotomy For Essential Tremor<br>Halpern 2019<br>ET-002; NCT01827904 | Long term follow-up of ET-003 RCT (Elias 2016) presenting efficacy and safety over 3 years.<br>Significant improvements in hand and postural tremor, disability and HRQoL observed at 6 months post procedure were maintained over 3 years. During the 3rd follow-up year, all previously noted adverse events remained mild or moderate, none worsened, two resolved, and no new adverse events occurred. | https://clinicaltrials.gov/ct2/show/NCT01827904 | 2019 |

** Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*

***Provide high level information including population numbers and whether patients are being recruited or in post-recruitment.*

****Date of when results will be made available (to the best of your knowledge).*

# PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

**19. List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the service (please attach a statement of clinical relevance from each group nominated):**

Neurosurgical Society of Australasia (NSA)

Australian and New Zealand Association of Neurologists (ANZAN)

The Royal Australian and New Zealand College of Radiologists (RANZCR)

*(Statements of Clinical Relevance from these organisations will be forwarded to the department as soon as possible)*

**20. List any professional bodies / organisations that may be impacted by this medical service (i.e. those who provide the comparator service):**

As for Q19.

**21. List the consumer organisations relevant to the proposed medical service (please attach a letter of support for each consumer organisation nominated):**

There are no formally incorporated consumer organisations for ET in Australia.

The 2018/19 Annual Report for the International Essential Tremor Foundation lists two points of contact for Australian patients.

https://www.essentialtremor.org/wp-content/uploads/2019/08/annual-report-2018-19.pdf

These people have been contacted by the applicant and we will forward any return correspondence if and when it becomes available.

**22. List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:**

N/A

**23. Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s):**

**Name of expert 1:** REDACTED

Telephone number(s): REDACTED

Email address: REDACTED

Justification of expertise: REDACTED

**Name of expert 2:**

Telephone number(s): REDACTED

Email address: REDACTED

Justification of expertise: REDACTED

*Please note that the Department may also consult with other referrers, proceduralists and disease specialists to obtain their insight.*

# PART 6 – POPULATION (AND PRIOR TESTS), INTERVENTION, COMPARATOR, OUTCOME (PICO)

***PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION***

**24. Define the medical condition, including providing information on the natural history of the condition and a high level summary of associated burden of disease in terms of both morbidity and mortality:**

ET is a chronic, progressive neurological condition characterised by rhythmic and oscillatory tremors of the upper extremities, not attributable to another cause (e.g. Parkinson's disease). With an estimated prevalence of ~4% in adults older than age 40, ET is one of the most common neurological disorders among adults. with higher prevalence rates observed among the elderly (Louis 2010).

In the past, ET has been thought of as a monosymptomatic disorder, characterised by kinetic arm tremor; however, it is now understood to be a clinically heterogeneous condition. In 2018, an updated consensus statement from the task force on tremor of the International Parkinson and Movement Disorder Society redefined ET as a syndrome (Bhatia, 2018). The classification was an attempt to recognise the heterogeneity of symptoms, which are unified only by the presence of action tremor in the arms. In the new criteria, ET is defined as an isolated tremor syndrome with only action tremor present for at least three years. The presence of tremor in other locations such as the legs, head, or voice is allowed. Tremors that have been present for less than three years are identified as isolated postural or kinetic tremors. In addition, no signs of other neurologic disease such as dystonia, ataxia, or parkinsonism are allowed to be designated as essential tremor (Shankar, 2019).

At disease onset, ET most commonly affects the upper limbs. Symptoms initially manifest with one hand being dominant, before progression to bilateral tremor of both hands within 1–2 years. However, the tremor generally remains slightly asymmetric with greater amplitude on the dominant side (Louis 1998). Tremor may eventually progress to other body parts, including the lower limbs, head, face and voice (Elble 2013). Additional motor problems may develop, including mild gait ataxia with increased risk for falls (Benito-León 2011). These symptoms can interfere with the ability to perform ADL such as drinking, shaving, dressing, handwriting and drawing. More than 90% of ET patients who seek medical attention report disability (Louis 2001) and severely affected patients are frequently unable to feed or dress themselves (Critchley 1949). Between 15% and 25% of patients are forced to retire prematurely, and 60% choose not to apply for a job or promotion because of uncontrollable shaking (Bain 1994).

In addition to motor-related symptoms, ET may be associated with non-motor sequelae, such as cognitive and sensory impairments (Benito-León 2014; Clark 2018). Case-control studies have shown that patients with ET may develop sleep disturbances, depressive symptoms, mild cognitive impairment [MCI], and dementia (Benito-León 2011; Bermejo-Pareja 2011; Louis 2012; Sengul 2015). The motor and non-motor related impairments associated with ET further impact functional, physical and psychosocial disability (Elble 2013).

ET is a progressive disease; the tremor gradually worsens with time. This, along with the accumulation of the co-morbidities noted above, result in both a functional decline and increased frailty (Louis 2011). As well as worsening with age, the symptoms of ET are known to be negatively affected by stress, tiredness, hunger, and extreme temperatures (NICE 2019).

For patients with tremor affecting ADL or HRQoL, medical therapy can help patients to control their symptoms; however, pharmacological therapy rarely achieves complete tremor control (Hedera 2013). Nonselective beta blockade with propranolol is the mainstay of treatment. Propranolol is contraindicated for several conditions, including asthma, diabetes mellitus and unstable heart failure, thus restricting the eligibility of many patients (Benito Leon 2006). Anti-epileptic medicines such as primidone and gabapentin are equally effective though are less frequently used due to the risk of side effects such as ataxia, vertigo, and acute toxic reactions (Zesiewicz 2005). Muscle relaxants such as alprazolam may also be considered.

It is estimated that 30-50% of patients are completely resistant to first line pharmacological therapy, with drug tolerance occurring in a further 13% of patients after chronic treatment (Koller 1989; Zesiewicz 2011). For these medically refractory patients, surgical interventions e.g. deep brain stimulation (DBS) offer the only chance of functional improvement.

Evidence for mortality in ET is limited, although a population-based study demonstrated there to be an increased risk of death with ET compared with the general population (RR = 1.59, 95% CI = 1.11 to 2.27, p = 0.01) (Louis 2007). This was further supported by a recent prospective longitudinal study of cognitive function in ET, which identified a number of independent predictors of mortality in elderly patients with ET. Those who died during the follow up period were found to have higher baseline Clinical Dementia Rating (CDR) scores and greater gait disturbance scores (GDS) and more depressive symptoms (Zubair 2018).

**25. Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed medical service, including any details of how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the service:**

It is proposed that eligibility for MRgFUS should be limited to adults under the care of a neurologist, who have medically refractory essential tremor, where the patient's symptoms cause severe disability.

For patients in whom tremor is causing significant functional or social disability, pharmacological intervention would be the first line of therapy. In Australia, this would typically comprise propranolol or primidone with other drugs such as gapapentin, alprazoloam and topiramate available where first line drugs are contraindicated or not tolerated. Patients who fail to derive adequate benefit from pharmacological treatment of ET, are considered to be medically refractory.

*The Applicant acknowledges that the definition of failure to derive adequate benefit to treatment is open to interpretation. There are currently no set guidelines that define the duration of treatment or thresholds of benefit when defining medically refractory essential tremor. It should, however, be noted that the decision to undergo MRgFUS would not be undertaken lightly, and it is likely that most patients would trial a range of pharmacologic therapies before considering the procedure. Similarly, it is highly probable that the majority of patients who currently undergo DBS for ET have medically refractory disease, despite the fact that this is not an explicit requirement in the MBS item descriptor.*

Following failure to achieve an adequate response to pharmacological therapy, patients are typically referred to a neurologist within a movement disorder clinic for assessment of suitability for therapeutic interventions such as DBS. At present, DBS is the only reimbursed intervention for patients with medically refractory ET. The MBS item descriptors for DBS (MBS item numbers 40850, 40851, 40852, 40854, 40856, 40858, 40860, 40862) specify that DBS should be used in patients with "ET or dystonia where the patient's symptoms cause severe disability". As DBS is the main comparator proposed in this application, it was considered appropriate to also limit the population eligible for treatment with MRgFUS to those whose symptoms cause severe disability.

Under the proposed listing, eligibility for MRgFUS therapy can only be determined by a neurologist. Once MRgFUS is prescribed, the patient will be referred to a qualified physician working as part of the treatment team for an assessment of their suitability for and the undertaking of MRgFUS. Post-procedure follow-up consultations would be provided by a neurologist.

**26. Define and summarise the current clinical management pathway *before* patients would be eligible for the proposed medical service (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway up to this point):**

The point of entry for care for ET patients is typically a GP who makes a diagnosis based on medical history and symptomatology. A full examination and blood test may be conducted to rule out other causes of tremor.

Under the care of their GP, patients in whom tremor is causing significant functional or social disability would initiate treatment with a pharmacological agents including beta-blockers (e.g.propranolol), anti-epileptic agents (e.g. primidone) or anti-anxiety medications. Upon failure to achieve an adequate response with first line treatment, patients may switch to an alternative drug. Second line treatment may also include muscle relaxants such as alprazolam or anti-epileptic agents such as gabapentin or topiramate.

If after further evaluation, patients are unable to achieve satisfactory symptom control with optimised medical therapy or if they are found to be refractory and/or intolerant to medical intervention with symptoms causing significant disability or impact on quality of life, patients are considered to have medically refractory ET (MRET).

*Treatment strategies for MRET*

Once considered medically refractory, patients are typically referred to a neurologist for ongoing assessment of severity and treatment. Treatment of medically refractory ET may often include persisting with pharmacological therapy as described above (optimised medical therapy). Deep Brain Stimulation (DBS) may also be considered in this difficult to treat population. As an invasive neurosurgical procedure, DBS is usually considered as a last-line therapeutic option. This is reflected by the relatively low uptake of DBS in Australia for the indication of ET. As discussed in Part 7, it is estimated that there were 245 DBS procedures performed, of which expert opinion suggests ~25% are related to the treatment of ET (*approximately 61 cases/year*). This estimate is similar to the total umber of patients expected to undergo DBS in MSAC assessment 1109. A survey of medication usage patterns among ET patients, which showed that 33% of patients who were receiving medication for ET had attempted four or more medications in their attempt to obtain relief (Diaz 2010); those who eventually underwent surgery for ET, had attempted a mean of six medications.

After initial appraisal, patients may undergo an extensive work up to assess suitability for surgery in a movement disorder clinic by a specialist team, which includes a movement disorder neurologist and neurosurgeon. The team may also include other specialists such as a movement disorders nurse, movement disorders neurologist, neuropsychiatrist, and neuropsychologist, depending on the team's usual protocol. This process aims to determine the likely benefit and risks of performing each type of procedure on an individual basis. DBS may be performed unilaterally or bilaterally; however as both procedures are performed at the same time many patients elect to undergo bilateral surgery due its superior clinical effectiveness. This is reflected in the Medicare utilisation statistics for DBS, which show that in 2018 226 bilateral procedures were performed (MBS item 40851) compared to 19 unilateral procedures (MBS item 40850). By comparison, MRgFUS is usually performed unilaterally due to the requirement that bilateral procedures must be separated by a minimum period of 6 months, and a high level of clinical efficacy is achieved by treating the dominant side only.

For those contraindicated or not suitable for surgery, patients will continue to be managed through best supportive care (BSC). This may include continued optimised medical therapy, as described above, despite its limited efficacy where no alternative options are available.

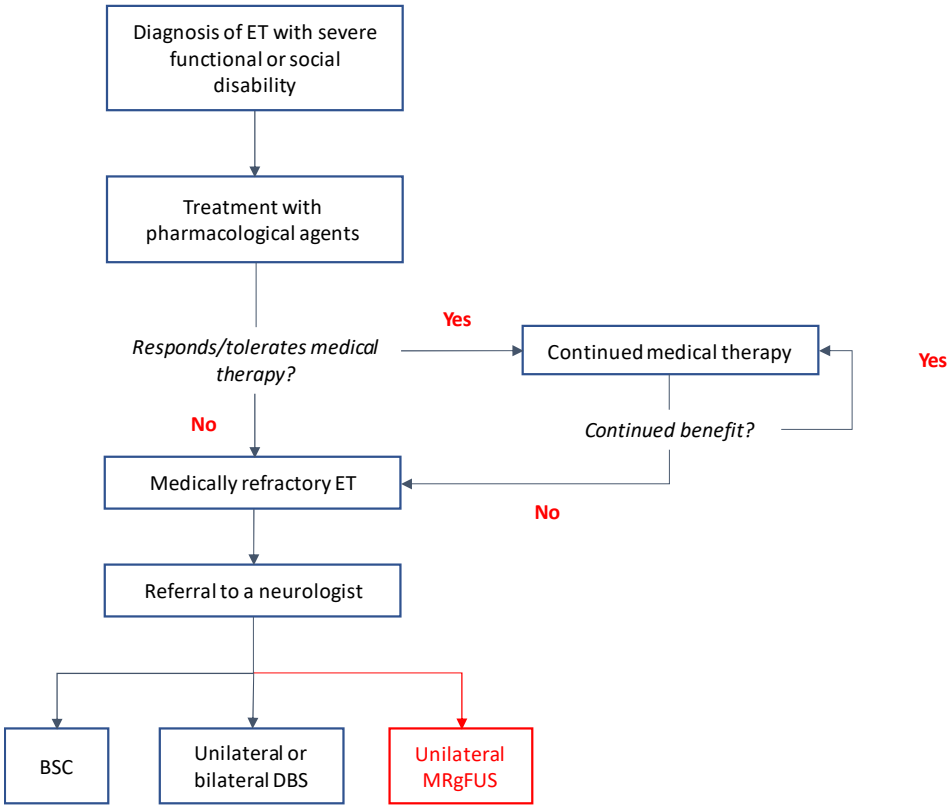


**Figure 1 Proposed clinical management pathway**

***PART 6b – INFORMATION ABOUT THE INTERVENTION***

**27. Describe the key components and clinical steps involved in delivering the proposed medical service:**

The procedure is performed by a physician and takes approximately 3-4 hours. A neurologist is also present to perform intraoperative clinical evaluations throughout the procedure. A radiologist is also present to perform the intraoperative MRIs.

The procedure can be considered to comprise four stages as follows:

1. Patient preparation

Several days before treatment, a CT scan is done to detail the shape, thickness and density of the patient's skull and confirm suitability for the procedure. A pre-operative MRI is also performed.

On the day of treatment, the patient's head is shaved, and a local anaesthetic is applied for affixing the stereotactic frame. The patient is positioned on the treatment bed with his/her head in the Exablate Neuro helmet. Cold water is circulated around the scalp.

2. Planning and target verification

Intraoperative (fused) MRI images are taken to plan the treatment and identify the target.

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

3. Treatment

The focused ultrasound treatment consists of up to 1024 ultrasound waves precisely converging at the target in the VIM. At the focal point, temperatures increase to near 140°F/60°C, causing thermal ablation

of the target tissue. The treatment is continuously guided by MRI for real-time thermal feedback of temperature changes at the target as well as non-focal temperature trends. The treatment is unilateral, generally treating the dominant hand.

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

4. Assessment

Treatment outcome is confirmed through neurological assessments as well as using a post-treatment scan immediately post-procedure. Most patients experience an immediate reduction in their tremor and will return to normal daily activities the following day.

Following successful completion of the procedure, the patient is required to stay overnight in the general ward for observation (4 hourly). Patients are required to undergo an MRI at 3 and/or 6 months follow up. No other monitoring of the patient is required.

Contralateral treatment

In Australian clinical practice currently, MRgFUS is provided as a unilateral treatment. Treatment of the contralateral side may be performed after a minimum of 6-12 months should the risk-benefit profile be favourable in the opinion of the treating team. Should the patient experience a recurrence of tremor, the patient would require consultation with the treating physician to determine suitability for retreatment. Retreatment is permitted once only per patient per side.

**28. Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?**

No, the proposed medical service does not include a registered trademark.

**29. If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?**

MRgFUS therapy offers a new approach to managing medically refractory ET where the patient's symptoms cause severe disability.

**30. If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e. accessibility, dosage, quantity, duration or frequency):**

At the moment, only one centre in Australia currently offers MRgFUS for the treatment of medically refractory ET. Due to the capital costs of the technology, it is anticipated that MRgFUS will be limited to only a very small number of centres, thereby potentially limiting accessibility to some patients.

Currently, MRgFUS is intended to be used once on the dominant affected side, thereby providing substantial and durable benefits in quality of life as supported by the clinical evidence. Following the procedure, a single post-operative MRI scan is performed. No further evaluations are required. This is in contrast to DBS for which regular follow up appointment s are required for monitoring, adjustment of hardware settings, and where replacement of leads and other hardware components are expected over time.

**31. If applicable, identify any healthcare resources or other medical services that would need to be delivered at the same time as the proposed medical service:**

Several days before treatment, a CT scan is done to detail the shape, thickness and density of the patient's skull and confirm suitability for the procedure. A pre-operative MRI is also performed.

Thermal ablation of the targeted tissue using MRgFUS is continuously guided by real-time MRI, in the presence of the treating team. As MRgFUS is an inpatient procedure, it is expected that operating rooms and other relevant infrastructure would be provided by the hospital.

Patients can be called upon to undergo an MRI at 3 and/or 6 months follow up to assess lesion formation and dynamics.

**32. If applicable, advise which health professionals will primarily deliver the proposed service:**

A trained physician is required to deliver the proposed service. A movement disorder specialist present at the procedure will provide intraoperative clinical evaluation.

**33. If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:**

Not applicable.

**34. If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:**

The applicant proposes that there should not be any limitations on who will be able to deliver the proposed service.

Whilst the item numbers described in PART 8 below identify tasks and MBS fees for the neurology, neurosurgery and radiology components of the procedure. It is feasible – and indeed probable – that over time (as physicians become more adept at executing the procedure) the tasks may be performed by, and fees reimbursed to, physicians of any of the three disciplines mentioned. That is to say, the three item numbers proposed for the intraoperative component of MRgFUS in PART 8 will be performed and charged to the MBS, however, it may be the case that they are performed and charged by only two physicians.

**35. If applicable, advise what type of training or qualifications would be required to perform the proposed service, as well as any accreditation requirements to support service delivery:**

A copy of Insightec's training plan is attached to this application (Attachment B)

**36. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select <u>ALL</u> relevant settings):**

- ☒ Inpatient private hospital (admitted patient)
- ☒ Inpatient public hospital (admitted patient)
- ☐ Private outpatient clinic
- ☐ Public outpatient clinic
- ☐ Emergency Department
- ☐ Private consulting rooms - GP
- ☐ Private consulting rooms – specialist
- ☐ Private consulting rooms – other health practitioner (nurse or allied health)
- ☒ Private day surgery clinic (admitted patient)
- ☐ Private day surgery clinic (non-admitted patient)
- ☒ Public day surgery clinic (admitted patient)
- ☐ Public day surgery clinic (non-admitted patient)
- ☐ Residential aged care facility
- ☐ Patient's home
- ☐ Laboratory
- ☐ Other – please specify below

Specify further details here

**(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:**

The MRgFUS procedure is to be provided in properly trained facilities.

**37. Is the proposed medical service intended to be entirely rendered in Australia?**

- ☒ Yes
- ☐ No – please specify below

***PART 6c – INFORMATION ABOUT THE COMPARATOR(S)***

**38. Nominate the appropriate comparator(s) for the proposed medical service, i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system (including identifying health care resources that are needed to be delivered at the same time as the comparator service):**

Patients who have failed treatment with pharmacotherapy may be treated surgically, with lesional surgery or DBS. In lesional surgery (open thalamotomy), cells in the thalamus are ablated using a probe inserted into a small hole drilled into the skull. By comparison, DBS involves inserting a permanent electrode into the thalamus or other region causing tremor. This is then connected via a wire to a pacemaker box located in the chest region. In Australian clinical practice, DBS is generally preferred over lesional surgery, as it can be reversed, it leaves little or no residual damage, and it is adjustable with the use of a programmable stimulator. Nevertheless, DBS is associated with risks, including intracranial bleeding and infection, as well as mispositioned electrodes, the need to replace the battery periodically, and hardware issues such as lead breakage. Only DBS is funded through Medicare and as such, it is considered the primary comparator for the submission.

It is, however, acknowledged that there may be a group of medically refractory ET patients who are currently receiving BSC because they are unwilling to accept the risks associated with DBS or are contra-indicated for the procedure. MRgFUS offers these patients a treatment option that does not require burr hole craniotomy, craniectomy or general anaesthesia. As such, BSC may be a potential secondary comparator in a subgroup of the proposed population.

As per the clinical algorithm shown in Figure 1, the positioning of MRgFUS will be in line with DBS and BSC. That is, for use in patients shown to be refractory or intolerant to medical therapy, and whose symptoms cause severe disability.

As noted previously, although MRgFUS is used primarily as a unilateral procedure in current clinical practice, the comparator comprises both unilateral and bilateral DBS. This reflects the fact that bilateral MRgFUS requires a separate procedure to be performed on the contralateral side at least 6 months later, whereas bilateral DBS may be performed concurrently. As most of the clinical benefits associated with MRgFUS treatment are derived by treating the dominant side, the costs and risks of a treating the contralateral side are often thought to outweigh the incremental benefits.

**39. Does the medical service (that has been nominated as the comparator) have an existing MBS item number(s)?**

☒ Yes (please list all relevant MBS item numbers below)
☐ No

Although MRgFUS is performed unilaterally, the comparator for MRgFUS would comprise both unilateral and bilateral DBS (as discussed in the response to Question 38) for which the following MBS items are relevant: 40850, 40851, 40852, 40854, 40856, 40858, 40860, 40862.

MBS items 40850 (unilateral DBS) and 40851 (bilateral DBS) describe the stereotactic procedure for the localisation and insertion of electrodes, MBS item 40852 describes the placement of the neurostimulator receiver or pulse generator, and MBS item 40860 describes target localisation, including intraoperative localisation. These items are claimed when the initial procedure is undertaken. The remaining MBS items (40854, 40856, 40858) are for the revision and replacement of electrodes, transmitters and leads, While MBS item 40862 is for programming the pulse generator.

| MBS item number | MBS item descriptor | Fee |
|---|---|---|
| 40850 | DEEP BRAIN STIMULATION (unilateral) functional stereotactic procedure including computer assisted anatomical localisation, physiological localisation including twist drill, burr hole craniotomy or craniectomy and insertion of electrodes | $2,300.70 |
| 40851 | DEEP BRAIN STIMULATION (bilateral) functional stereotactic procedure including computer assisted anatomical localisation, physiological localisation including twist drill, burr hole craniotomy or craniectomy and insertion of electrodes | $4,026.40 |
| 40852 | DEEP BRAIN STIMULATION (unilateral) subcutaneous placement of neurostimulator receiver or pulse generator | $346.05 |
| 40854 | DEEP BRAIN STIMULATION (unilateral) revision or removal of brain electrode | $534.80 |
| 40856 | DEEP BRAIN STIMULATION (unilateral) removal or replacement of neurostimulator receiver or pulse generator | $259.55 |
| 40858 | DEEP BRAIN STIMULATION (unilateral) placement, removal or replacement of extension lead | $534.80 |
| 40860 | DEEP BRAIN STIMULATION (unilateral) target localisation incorporating anatomical and physiological techniques, including intra-operative clinical evaluation, for the insertion of a single neurostimulation wire | $2,055.05 |
| 40862 | DEEP BRAIN STIMULATION (unilateral) electronic analysis and programming of neurostimulator pulse generator | $163.85 |

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

**40. Define and summarise the current clinical management pathway/s that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards, including health care resources):**

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

Once discharged, patients are required to return to their treating neurologist frequently for several months in order to have the stimulation adjusted and optimised. Doctors also must supervise reductions in patients' medications. After a few months, the number of medical visits usually decreases significantly, though patients are still required to return to have their stimulator checked regularly. In the Assessment Report for MSAC Application 1109 (DBS for dystonia and essential tremor), it was estimated that patients would require 25 programming visits per patient over ten years.

The life span of the pulse generator battery is typically 3-5 years requiring surgery for replacement.

Other complications that can arise requiring re-intervention include:

- Fracture or breakage of the wire or cable
- Battery failure
- Erosion of the cable or device through the skin
- Migration of the electrode in the brain due to failure of the anchor

A full clinical algorithm is presented in Attachment A.

**41. (a) Will the proposed medical service be used in addition to, or instead of, the nominated comparator(s)?**

☒ In addition to (i.e. it is an add-on service) MRgFUS will be used in addition to BSC
☒ Instead of (i.e. it is a replacement or alternative) MRgFUS will be used in place of DBS

**(b) If instead of (i.e. alternative service), please outline the extent to which the current service/comparator is expected to be substituted:**

Every patient receiving DBS for ET is a potential candidate for MRgFUS.

**42. Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service, including variation in health care resources (Refer to Question 39 as baseline):**

Compared with DBS, MRgFUS is expected to reduce the hospital length of stay, result in fewer follow up appointments (related to the programming of DBS hardware required) and reduce the number of reinterventions due to replacement of DBS electrodes, batteries and other hardware over time. Given the lack of incision required to deliver the service, there would also be a reduction in health resources required to treat serious adverse events such as infections and wounds complications.

Compared with BSC, patients treated with MRgFUS may require more frequent follow up in the initial post-procedure period; however, in the longer term, the frequency of routine consultations is expected to be the same (if not lower in successfully treated MRgFUS patients).

***PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME***

**43. Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):**

The clinical evidence to support the clinical effectiveness of MRgFUS is described in PART 4. For the treatment of medically refractory ET, it is expected that MRgFUS is:

- Non-inferior with respect to clinical efficacy and non-inferior with respect to safety, compared with DBS.
- Superior with respect to clinical efficacy and inferior with respect to safety, compared with BSC.

It is expected that an MSAC application for MRgFUS would include a cost minimisation analysis against the primary comparator, DBS.

Given DBS has already been established as cost-effective against BSC. It is anticipated that an economic evaluation of MRgFUS against BSC will not be required. That is, assuming MRgFUS is proven to be non-inferior to DBS and with lower costs. It automatically follows MRgFUS would provide value for money relative to best supportive care.

**44. Please advise if the overall clinical claim is for:**

☒ Superiority When compared with BSC
☒ Non-inferiority When compared with DBS (albeit with a less invasive procedure and greater convenience for patients)

**45. Below, list the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be specifically measured in assessing the clinical claim of the proposed medical service versus the comparator:**

**Safety Outcomes:**

Serious adverse events (Neurologic and physical)

Procedure-related adverse events

Intraprocedural sensations or events

AEs/complications

**Clinical Effectiveness Outcomes**

Tremor severity (measured by Clinical Rating Scale for Tremor [CRST]) and sub-scores (hand, postural, action)

Disability (measured by CRST Part C)

Quality of life/Activities of daily living (measured using Quality of Life in Essential Tremor Questionnaire [QUEST])

Recurrence of tremor

# PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

**46. Estimate the prevalence and/or incidence of the proposed population:**

ET is among the most prevalent movement disorders (Louis 2010; Zesiewicz 2015), and increases markedly with age, and exponentially with advanced age (Louis 2019). A 2010 meta-analysis of population-based prevalence studies found worldwide prevalence to be 4.6% for ages ≥65 years, increasing to be as high as 22% for ages ≥95 years.(Louis 2010).

Despite this high prevalence, the precise number of cases of ET is difficult to determine, since the variable clinical presentation often leads to misdiagnosis (Jain 2006; Espay 2017). A summary of prevalence estimates identified in the literature are presented in Table 1. To date, no estimates are available for Australia.

**Table 1 Prevalence estimates of ET**

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

The burden of the high prevalence of ET is worsened by the substantial proportion of ET patients who are refractory to medication. For these patients, the only neurosurgical procedure currently reimbursed in Australia is DBS. DBS is currently listed on the MBS for the treatment of PD, ET or dystonia, with primary treatment falling under MBS items 40850 (unilateral DBS) and 40851 (bilateral DBS).

Historical (5-year) utilisation of DBS is presented in Table 2, showing an estimated 250 DBS procedures annually, mostly bilateral. Expert opinion has indicated that approximately 25% of DBS procedures performed in Australia within a private hospital setting are used to treat severe disabling ET (N=65), with the remainder performed for PD or dystonia.

It is acknowledged that there may also be a population with severe disabling, medically refractive ET who do not wish to undergo DBS due to the invasive nature of the procedure. As such, MBS funding of MRgFUS may result in a number of patients electing to have MRgFUS who would otherwise not have chosen to undergo a neurosurgical procedure and are currently treated with BSC. The potential size of this additional population can be estimated from the underling epidemiology/prevalence of sever disabling ET and the capacity constraints of the healthcare system in an MSAC Assessment Report

**Table 2 Utilisation of MBS items for deep brain stimulation**

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

**47. Estimate the number of times the proposed medical service(s) would be delivered to a patient per year:**

MRgFUS is usually performed as a unilateral procedure intended to treat the dominant affected side in severe medically refractory essential tremor. It is anticipated that the proposed service would be delivered once per patient on the dominant side. The contralateral side may be treated with a minimum of 6 months between procedures. However, as most of the clinical benefits associated with MRgFUS treatment are derived by

treating the dominant side, the costs and risks of a treating the contralateral side are often thought to outweigh the incremental benefits.

While recurrence of tremor may occur after MRgFUS, long term data up to five years shows this to be a rare occurrence (Park et al., 2019).

Accordingly, it is expected that, on average, the vast majority of patients will have one procedure performed in year 1 and no procedures thereafter.

**48. How many years would the proposed medical service(s) be required for the patient?**

Not applicable. It is anticipated that for most patients, MRgFUS will comprise a single procedure per lifetime.

**49. Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:**

The uptake of MRgFUS will be limited by accessibility given that only one centre currently provides this service requiring patients outside of the Sydney metropolitan area to travel for treatment. Based on expert opinion and current levels of utilisation, it is anticipated that approximately 45-50 patients will be treated in the first year.

**50. Estimate the anticipated uptake of the proposed medical service over the next three years factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors) as well as provide commentary on risk of 'leakage' to populations not targeted by the service:**

Current utilisation of DBS (245 procedures per annum of which the majority are for Parkinson's Disease) provides a reasonable estimate for the potential demand for MRgFUS at less than 100 patients per annum. In the short term there may be a higher prevalent pool of patients who have decided against DBS but would use MRgFUS should it become funded.

Supply side constraints include access to the availability of the MRgFUS equipment and the specialist physicians to perform the procedure.

While MRgFUS is perceived to be minimally invasive in comparison with DBS, the decision to undergo MRgFUS for the treatment of ET is unlikely to be taken lightly given the irreversible nature of the procedure. In light of this, "leakage" to less severe or non-medically refractory patients is low. The low risk of leakage is a view shared by the Neurosurgery and Neurology Clinical Committee in the MBS taskforce review: "the Committee believes that existing ethical and regulatory restrictions on psychosurgery (and the invasiveness of the surgery itself) will prevent inappropriate use of this item. Patients are also subject to careful selection by neurologists and neurosurgeons, and only a small number of neurosurgeons are able to perform this procedure in Australia, making inappropriate use even less likely."

# PART 8 – COST INFORMATION

**51. Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:**

The likely cost will be made up of the fee and the inpatient hospital admission. There are no prostheses involved however the disposable patient kit (described in question 12) will require a funding stream and could be included in Part C of the prosthesis list.

As discussed above (Question 34), the breakdown of costs (and MBS fees) is described in terms of neurosurgery, neurology and radiology components. However, it is not intended that these MBS items are restricted for use only by neurosurgeons, neurologist or radiologists respectively. Rather, the breakdown reflects the cost of performing the service, irrespective of the number and qualification of the specialist physicians providing it.

It is anticipated the cost of a hospital admission for MRgFUS would incorporate amortisation and maintenance of capital equipment, operating theatre costs and inpatient stay. An overall cost breakdown for delivery of MRgFUS procedure (and compared to DBS) is presented in Table 3.

**Table 3 Comparison of approximate cost profile for MRgFUS and DBS procedure**

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

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

**52. Specify how long the proposed medical service typically takes to perform:**

The MRgFUS procedure typically takes 3-4 hours. This is similar to the procedure time for DBS, suggesting the item descriptors for unilateral and bilateral DBS are likely to be relevant benchmarks.

**53. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and medical service usage characteristics that would define eligibility for MBS funding.**

MBS item descriptors for radiology, neurology and neurosurgery components of the service are presented below. These MBS item numbers are presented in the context of the services performed as described in Question 27. Namely:

- Patient preparation and pre-surgical planning
- Planning and target verification
- Treatment
- Assessment

Patient preparation and pre-surgical planning

Several days / months before treatment, a specialised CT scan is performed to detail the shape, thickness and density of the patient's skull. The skull density ratio (SDR) is calculated by the radiologist to assess whether sufficient energy can be delivered during the MRgFUS procedure and confirm patient suitability. A pre-operative MRI scan is also performed to exclude contraindications, assess the patient's anatomy and plan the treatment. The pre-operative MRI scan is fused with the CT to more accurately guide treatment. Patients with suitable imaging evaluations are progressed towards planning for the procedure.

New MBS item number requested for MRI of the brain to assess suitability.

The proposed wording and fee of this item number is based on other MRI Scan of the Head services

| | | |
|---|---|---|
| | | Category 5 – DIAGNOSTIC IMAGING SERVICES |
| | Group | I5 – Magnetic Resonance Imaging |
| | Subgroup | 1 – Scan of Head – For Specific Conditions |
| 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:<br><br>- assessment of suitability for treatment of essential tremor with MRI guided focussed ultrasound<br><br>Essential tremor where:<br>(a) Symptoms cause severe disability, and<br>(b) Tremor has proven refractory to, or recurred following, maximal medical therapy<br><br>Bulk bill incentive<br><br>(Anaes.)<br>Fee: $403.20 Benefit: 75% = $302.40 85% = $342.75 | | |

Planning and target verification

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

New MBS item number requested for MRI of the brain and associated planning reports.

The proposed wording and fee of this item number is based on another MBS item for planning of stereotactic neurosurgery (MBS item 63010). It may also be the case that a new MBS item number for this service may not be required but provided here for completeness the Head services

| | | |
|---|---|---|
| | | Category 5 – DIAGNOSTIC IMAGING SERVICES |
| | Group | I5 – Magnetic Resonance Imaging |
| | Subgroup | 1 – Scan of Head – For Specific Conditions |
| 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:<br><br>- stereotactic scan of brain, with Fiducials in place, for the sole purpose to allow planning for MRI guided focussed ultrasound<br><br>Bulk bill incentive<br><br>(Anaes.)<br>Fee: $336.00 Benefit: 75% = $252.00 85% = $285.60 | | |

Note: This proposed MBS item is identical to 63010 except MRI guided focussed ultrasound replaces the words "stereotactic neurosurgery"

Treatment/ Intraoperative procedure

The intraoperative procedure requires three item numbers. One for the neurosurgery, neurology and radiology services provided respectively. Although, as noted previously, it is intended that there be no restrictions placed on the specialty of the physician(s) performing these services (provided they are adequately trained and qualified).

New MBS item number requested for neurology services provided during the procedure

The MBS item wording and fee is based on the analogous service provided during deep brain stimulation procedure (MBS item 40860)

| Category 3 - THERAPEUTIC PROCEDURES | |
|---|---|
| Group | # - #### |
| Subgroup | # - #### |
| Subheading | ## - #### |

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

Multiple Operation Rule

(Anaes.) (Assist.)

Fee: $2,055.05 Benefit: 75% = $#####

New MBS item number requested for neurosurgery services provided during the procedure

The MBS item wording and fee is based on the for the surgical component (i.e. excluding placement of the generator and revision/programming) deep brain stimulation procedure (MBS items 40850 and 40851)

| Category 3 - THERAPEUTIC PROCEDURES | |
|---|---|
| Group | # - #### |
| Subgroup | # - #### |
| Subheading | ## - #### |

MRI GUIDED FOCUSSED ULTRASOUND (unilateral) procedure including computer assisted anatomical localisation, physiological localisation, and lesion production in the basal ganglia, brain stem, thalamus or deep white matter tracts, for the treatment of:

Essential tremor where:

(a) Symptoms cause severe disability, and

(b) Tremor has proven refractory to, or recurred following, maximal medical therapy

Multiple Operation Rule

(Anaes.) (Assist.)

Fee: TBD (Approx $2301 to $4026)[a] Benefit: 75% = $#####

New MBS item number requested for radiology services provided during the procedure

Intraoperative (fused) MRI images are taken to plan the treatment and identify the target.

There do not seem to be any suitable, analogous MBS items upon which to base the wording and MBS fee for this service. It is anticipated the fee would be higher than a single MRI Scan of the Head due to the time the radiologist is with the patient and the number of scans taken during the procedure. A suitable fee will be proposed and justified in the ADAR.

| | |
|---|---|
| | Category 3 - THERAPEUTIC PROCEDURES |
| Group | # - #### |
| Subgroup | # - #### |
| Subheading | ## - #### |

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

Multiple Operation Rule

(Anaes.) (Assist.)

Fee: $##### Benefit: 75% = $#####

Assessment

Treatment outcome is confirmed using post-treatment MRI scans at various intervals

New MBS item number requested for MRI of the brain to assess patient outcomes and exclude potential complications.

The proposed wording and fee of this item number is based on other MRI Scan of the Head services

| | |
|---|---|
| | Category 5 – DIAGNOSTIC IMAGING SERVICES |
| Group | I5 – Magnetic Resonance Imaging |
| Subgroup | 1 – Scan of Head – For Specific Conditions |

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

- assessment of treatment outcomes following MRI guided focussed ultrasound procedure

Bulk bill incentive

(Anaes.)
Fee: $403.20 Benefit: 75% = $302.40 85% = $342.75

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