

ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Magnetic Resonance-Guided Focused Ultrasound Neurosurgery for Essential Tremor: A Health Technology Assessment

KEY MESSAGES

What Is This Health Technology Assessment About?

Essential tremor is the most common movement disorder and most often affects the dominant hand and arm. As the tremor gets worse, it can negatively impact quality of life. Medication is the first treatment, but it does not work for many people. The next treatment option is neurosurgery (brain surgery). Presently in Ontario, the neurosurgery options generally available are invasive procedures that involve craniotomy (opening the skull). Magnetic resonance-guided focused ultrasound (MRgFUS) neurosurgery is a new, noninvasive surgical technology for the treatment of essential tremor. Because MRgFUS neurosurgery is noninvasive, it does not have the same surgical risks as invasive procedures. Thus, it may be an option for people who cannot undergo invasive surgery and for people who find the risks of invasive surgery, such as craniotomy, general anaesthetic, and implanted hardware, unacceptable.

We reviewed the evidence to evaluate the effectiveness and safety of MRgFUS neurosurgery, assessed the cost-effectiveness of MRgFUS neurosurgery compared with other surgical treatments, and calculated the budget impact of publicly funding MRgFUS neurosurgery. We also interviewed people with essential tremor to learn about their experiences and to gain an understanding of their preferences and values with regard to treatment options for essential tremor, including MRgFUS neurosurgery.

What Did this Health Technology Assessment Find?

The evidence shows that MRgFUS neurosurgery is generally safe and effective at reducing tremor severity, improving quality of life, and helping people get back to their daily activities. MRgFUS neurosurgery offers a treatment option for people with essential tremor who otherwise have none if medication fails, and it offers a noninvasive option for people considering surgery who cannot safely have invasive surgery or who find the risks of invasive surgery unacceptable.

For people with essential tremor who cannot undergo invasive neurosurgery, MRgFUS neurosurgery represents good value for money compared with no surgery. For people who can undergo invasive neurosurgery, MRgFUS neurosurgery appears to be one of several reasonable options. Publicly funding MRgFUS neurosurgery for the treatment of moderate to severe, medication-refractory essential tremor in Ontario would result in additional spending of \$1 million per year for the next 5 years.

People with essential tremor who had undergone MRgFUS neurosurgery reported positive experiences with the procedure and felt that it had improved their quality of life by substantially reducing their tremor.

HEALTH TECHNOLOGY ASSESSMENT AT HEALTH QUALITY ONTARIO

This report was developed by a multidisciplinary team from Health Quality Ontario. The lead clinical epidemiologist was Alexis Schaink, the lead health economist was Chunmei Li, the secondary health economist was Olga Gajic-Veljanoski, the Patient, Caregiver, and Public Engagement analyst was David Wells, and the medical librarian was Caroline Higgins.

The medical editor was Kara Stahl; others involved in the production of this report were Paul Kolodziej, Kellee Kaulback, Ana Laing, Claude Soulodre, Sarah McDowell, Andrée Mitchell, Vivian Ng, Anil Thota, Nancy Sikich, and Irfan Dhalla.

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The statements, conclusions, and views expressed in this report do not necessarily represent the views of the consulted experts.

Citation

TBD

^a Staff Neurologist and Co-director, Surgical Program, Morton and Gloria Shulman Movement Disorders Centre and Edmond J. Safra Program in Parkinson's Disease, Toronto Western Hospital–University Health Network; Associate Professor, Department of Medicine, Division of Neurology, University of Toronto Clinician Investigator, Krembil Research Institute

^b Finance Director and Senior Finance Lead, Diagnostic Partnerships, Pharmacy, IPAC; Director, JDML Research Office, University Health Network

^c Director and Senior Scientist, Physical Sciences Platform, Sunnybrook Research Institute; Director, Centre for Research in Image-Guided Therapeutics, Canada Research Chair in Imaging Systems and Image-Guided Therapy (Tier 1); Professor, Department of Medical Biophysics and Institute of Biomaterial and Biomedical Engineering, University of Toronto

^d Director, Morton and Gloria Shulman Movement Disorders Centre and Edmond J. Safra Program in Parkinson's Disease, Toronto Western Hospital–University Health Network, University of Toronto

^e Neurosurgeon, Sunnybrook Health Sciences Centre; Scientist, Sunnybrook Research Institute; Assistant Professor, Department of Surgery, University of Toronto; Associate Member, Institute of Medical Science, University of Toronto

^f Dan Family Chair of Neurosurgery, University of Toronto

^g Professor of Surgery (Neurosurgery), University of Toronto

^h Vice-President, Clinical Operations and Diagnostic Partnerships, University Health Network; Joint Department of Medical Imaging, University Health Network, Sinai Health System, Women's College Hospital; Laboratory Medicine Program, University Health Network; Department of Microbiology, Sinai Health System, University Health Network; Assistant Professor, Department of Medical Imaging, Faculty of Medicine, University of Toronto

ABSTRACT

Background

The standard treatment option for medication-refractory essential tremor is invasive neurosurgery. A new, noninvasive alternative is magnetic resonance-guided focused ultrasound (MRgFUS) neurosurgery. We aimed to determine the effectiveness, safety, and cost-effectiveness of MRgFUS neurosurgery for the treatment of moderate to severe, medication-refractory essential tremor in Ontario. We also spoke with people with essential tremor to gain an understanding of their experiences and thoughts regarding treatment options, including MRgFUS neurosurgery.

Methods

We performed a systematic review of the clinical literature published up to April 11, 2017, that examined MRgFUS neurosurgery alone or compared with other interventions for the treatment of moderate to severe, medication-refractory essential tremor. We assessed the risk of bias of each study and the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. We performed a systematic review of the economic literature and created Markov cohort models to assess the cost-effectiveness of MRgFUS neurosurgery compared with other treatment options, including no surgery. We also estimated the budget impact of publicly funding MRgFUS neurosurgery in Ontario for the next 5 years. To contextualize the potential value of MRgFUS neurosurgery as a treatment option for essential tremor, we spoke with people with essential tremor and their families.

Results

Nine studies met our inclusion criteria for the clinical evidence review. In noncomparative studies, MRgFUS neurosurgery was found to significantly improve tremor severity and quality of life and to significantly reduce functional disability (GRADE: very low). It was also found to be significantly more effective than a sham procedure (GRADE: high). We found no significant difference in improvements in tremor severity, functional disability, or quality of life between MRgFUS neurosurgery and deep brain stimulation (GRADE: very low). We found no significant difference in improvement in tremor severity compared with radiofrequency thalamotomy (GRADE: low). MRgFUS neurosurgery has a favourable safety profile.

We estimated that MRgFUS neurosurgery has a mean cost of \$23,507 and a mean quality-adjusted survival of 3.69 quality-adjusted life-years (QALYs). We also estimated that the mean costs and QALYs of radiofrequency thalamotomy and deep brain stimulation are \$14,978 and 3.61 QALYs, and \$57,535 and 3.94 QALYs, respectively. For people ineligible for invasive neurosurgery, we estimated the incremental cost-effectiveness ratio (ICER) of MRgFUS neurosurgery compared with no surgery as \$43,075 per QALY gained. In people eligible for invasive neurosurgery, the ICER of MRgFUS neurosurgery compared with radiofrequency thalamotomy is \$109,795 per QALY gained; when deep brain stimulation is compared with MRgFUS neurosurgery, the ICER is \$134,259 per QALY gained. Of note however, radiofrequency thalamotomy is performed very infrequently in Ontario. We also estimated that the budget impact of publicly funding MRgFUS neurosurgery in Ontario at the current case load (i.e., 48 cases/year) would be about \$1 million per year for the next 5 years.

People with essential tremor who had undergone MRgFUS neurosurgery reported positive experiences with the procedure. The tremor reduction they experienced improved their ability to perform activities of daily living and improved their quality of life.

Conclusions

MRgFUS neurosurgery is an effective and generally safe treatment option for moderate to severe, medication-refractory essential tremor. It provides a treatment option for people ineligible for invasive neurosurgery and offers a noninvasive option for all people considering neurosurgery.

For people ineligible for invasive neurosurgery, MRgFUS neurosurgery is cost-effective compared with no surgery. In people eligible for invasive neurosurgery, MRgFUS neurosurgery may be one of several reasonable options. Publicly funding MRgFUS neurosurgery for the treatment of moderate to severe, medication-refractory essential tremor in Ontario at the current case load would have a net budget impact of about \$1 million per year for the next 5 years.

People with essential tremor who had undergone MRgFUS neurosurgery reported positive experiences. They liked that it was a noninvasive procedure and reported a substantial reduction in tremor that resulted in an improvement in their quality of life.

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OBJECTIVE

This health technology assessment examines the effectiveness, safety, and cost-effectiveness of magnetic resonance-guided focused ultrasound (MRgFUS) neurosurgery for the treatment of moderate to severe, medication-refractory essential tremor. It also assesses the budget impact of publicly funding MRgFUS neurosurgery in Ontario and examines the experiences of people with essential tremor and their perspectives on treatment options, including MRgFUS neurosurgery.

BACKGROUND

Health Condition

Essential tremor is a benign, chronic, progressive condition of tremors (rhythmic, oscillatory, involuntary movements) that occur during rest or action, which is not attributed to another cause (e.g., Parkinson's disease).¹ Typically, essential tremor manifests in one or more of the upper limbs (in about 95% of cases), the head, trunk, or voice.² The condition is the most common movement disorder, estimated to affect 0.4% to 3.9% of the general adult population, with an increase in severity and prevalence with age.³ The average age of onset is 45 years; however, essential tremor can occur at any age, including adolescence and early adulthood.⁴ The condition tends to run in families.¹

Diagnosis and Assessment

There are several types of tremors and tremor-like syndromes, and these are classified based on their primary characteristics: affected area(s), frequency of oscillation (measured in Hertz [Hz]), accompanying features, age at onset, and rapidity of onset.⁵ Essential tremor is distinguished by middle- to high-frequency tremors (i.e., 4–12 Hz) at rest, during movement (kinetic), and when maintaining the body in a position against gravity (postural; e.g., holding arms outstretched).² The diagnostic workup may include brain imaging, tests such as electromyography (EMG; to determine the frequency of the tremor), and a complete medication history. A diagnosis of essential tremor is challenging, but is reached when the tremor characteristics fit the profile, there are no other neurological signs, and other types and causes of tremor have been ruled out.²

Tremor severity is evaluated by a person's assessment of the impact of essential tremor on their quality of life and via tools such as the Clinical Rating Scale for Tremors (CRST; an adaptation of the Fahn–Tolosa–Marín [FTM] Clinical Rating Scale for Tremor).⁶ These essential tremor-specific severity scales include three subscales—tremor; tasks of writing, drawing, and pouring; and activities of daily living—as well as global assessments by both patient and clinician.⁷

One component of the CRST is a spiral-drawing task, sometimes called the “Archimedes spiral.” This task is clinically useful, as people with essential tremor demonstrate a distinct tremor pattern and spiral diameter on this task.^{8,9} Repeated assessment can aid in evaluating tremor severity, tremor progression, and response to therapy. The CRST has been validated as sensitive to changes in essential tremor over time.⁷ Table 1 outlines the FTM scale and provides examples of the components of each subscale.⁷ (Note that the overall scoring of the CRST differs slightly from that of the FTM.)

Table 1: Summary of the Fahn–Tolosa–Marín Clinical Rating Scale for Tremor

Scale	Objective	Scoring (Examples of Meaning)
Part A	Quantifies tremor while holding posture, and with action/intention in nine body parts	0: None 1: Amplitude < 0.5 cm (slight, may be intermittent) 2: Amplitude 0.5–1.0 cm (moderate, may be intermittent) 3: Amplitude 1–2 cm (marked) 4: Amplitude > 2 cm (severe)
Part B	Action tremor of the upper extremities during writing, drawing, and water pouring	0: Normal 1: Mild (untidy, may cross lines, no spilling) 2: Moderate (consistent tremor but legible, crosses lines frequently, spills up to 10%) 3: Marked (illegible, great difficulty drawing, spills > 10–50%) 4: Severe (unable to keep pen on paper, complete drawing, or pour without spilling most of the water)
Part C	Functional disability, including speaking, eating, drinking, hygiene, dressing, working, and domestic tasks	0: Normal 1: Mild (spills food rarely, moves more carefully when doing tasks than the average person) 2: Moderate (unable to use spoon, able but many errors in dressing, hygiene, work tasks) 3: Marked (uses two hands to eat or for hygiene, unable to do regular job, requires assistance with dressing) 4: Severe (some words difficult to understand, needs help to feed, unable to do any fine movements, requires assistance for even gross motor tasks, unable to work)
Total	Overall assessment of severity and disability (parts A, B, and C), as well as each of clinician's and patient's subjective assessments of severity	Expressed as a percentage representing severity 1–24%: Mild disability 25–49%: Moderate disability 50–74%: Marked disability 75–100%: Severe disability

Source: Fahn et al, 1988.⁶

Current Treatment Options

There is no cure for essential tremor; however, treatments can help patients manage the symptoms. Many people live with essential tremor untreated for an extended period of time, often decades, not seeking treatment until tremor severity progresses to a point at which it interferes with daily life. Severe essential tremor is disabling, limiting a person's ability to perform routine activities of daily living, such as eating, writing, walking, and self-care, thus considerably impacting quality of life, the ability to work or participate in social activities, and independence.¹ Pharmacotherapy is the first-line treatment for essential tremor; the beta-blocker propranolol and the anticonvulsant primidone are most commonly trialed.^{1,10,11} However, as many as half of all people with essential tremor experience recurrent tremor or inadequate tremor control while taking medication, have contraindications to medication, or cannot tolerate the side effects of medication.¹¹

Although the exact pathophysiology of essential tremor is not well understood,¹² it is known to involve the cerebello-thalamo-cortical network.¹³ The area of the brain targeted during neurosurgery is typically the ventral intermediate nucleus of the thalamus or, less commonly, the cerebellothalamic tract.¹⁰

Two invasive neurosurgical treatment options are available for people with medication-refractory, disabling essential tremor: lesional surgery and deep brain stimulation. Lesional surgery involves creating a permanent injury to the part of the brain causing the tremor, whereas deep brain stimulation involves implanting permanent electrodes into the affected brain areas to inhibit neural activity.¹¹ Although these surgical techniques can alleviate tremor in about 40% to 80% of people with essential tremor who undergo them, there are risks involved with each procedure that must be considered for each person.¹⁰

The principal lesional surgery for essential tremor is unilateral thalamotomy, in which neurons in the thalamus on one side of the brain are destroyed. This procedure has historically been performed via craniotomy (opening the skull). During the surgery, a probe is inserted to deliver radiofrequency electrical current to heat the target site and create a lesion, a method called ablation.¹⁰ The patient is kept awake so that the clinical team can assess the accuracy of the target location before creating a permanent lesion. Radiofrequency thalamotomy has been in practice since the mid-twentieth century and was the main surgical option for essential tremor prior to the introduction of other surgical techniques.¹⁰ As an invasive surgery, radiofrequency thalamotomy is inappropriate for people with surgical contraindications (e.g., unstable cardiac disease) and has inherent risks, including hemorrhage, infection, and seizure.¹⁰

Thalamotomy can also be performed noninvasively by focusing radiation beams through the skull via a technology called Gamma Knife. The effects of Gamma Knife thalamotomy, in terms of both tremor control and adverse effects, do not appear until weeks or months after the procedure. Importantly, people who undergo the procedure have variable responses to radiation, and there is a risk of progressive neurological deficits associated with the radiation.^{14,15} Documented procedure-related complications include mild numbness, hemiparesis (paralysis on one side of the body), dysphagia (difficulty swallowing), and death.¹⁴ Gamma Knife thalamotomy also relies entirely on anatomical imaging to identify the target area in the brain. Further, in contrast to all other surgeries for essential tremor, this procedure does not allow for testing to refine and confirm the correct target location prior to ablation.¹⁵ There may be a role for Gamma Knife thalamotomy in rare cases of essential tremor; for example, elderly people who cannot undergo an invasive procedure such as deep brain stimulation.^{14,15} However, a shortage of long-term data on effectiveness and safety led the American Academy of Neurology to conclude that the evidence is insufficient to make a recommendation regarding the use of Gamma Knife thalamotomy for the treatment of essential tremor.¹⁶

Deep brain stimulation is the current standard of care for the neurosurgical treatment of essential tremor, as it is considered reversible and adjustable. This procedure is an invasive, nondestructive surgery that can be applied unilaterally (to one side of the brain) or bilaterally (to both sides of the brain).¹⁷ This is different from lesional surgery, which is typically performed unilaterally. Deep brain stimulation involves craniotomy and the implantation of permanent electrodes into the brain that electrically stimulate the target area, inhibiting neural activity and thus alleviating the tremor.¹⁸ As with thalamotomy, the patient is kept awake so that the clinical team can assess the accuracy of the target location. In a subsequent surgery, a pulse generator (a device similar to a pacemaker) is surgically implanted below the clavicle to adjust the stimulation delivered by the implanted electrodes.¹⁷ A unique advantage of deep brain stimulation over lesional surgery is that tremor control and adverse effects can be titrated

(adjusted) or reversed by adjusting the stimulation settings.¹⁸ The implanted pulse generator must be programmed by a clinician to optimize the stimulation settings, and the battery of the generator must be replaced at intervals of 2 to 5 years.¹⁷ In 2005, the Ontario Health Technology Advisory Committee recommended increased access to deep brain stimulation in Ontario for people with medication-refractory movement disorders, including essential tremor.¹⁹

Adverse effects of both radiofrequency thalamotomy and deep brain stimulation can arise from inaccurate target localization, acute swelling in response to surgery, or the size of the lesion created during radiofrequency thalamotomy.²⁰ These can be transient or permanent and include ataxia (alterations in control of body movements), paresthesias (bodily sensations of burning, tingling, or pricking), dysarthria (slowed or slurred speech), hemorrhage (bleeding in the brain), or seizures.¹⁰ The risk of intracranial hemorrhage associated with invasive stereotactic neurosurgeries (including radiofrequency thalamotomy and deep brain stimulation) ranges between 1% and 4%.^{20,21}

The few studies comparing radiofrequency thalamotomy with deep brain stimulation have found that both procedures are effective in controlling tremor in essential tremor, both in the short term^{20,21} and 5 years post-surgery.²² Despite their similar effectiveness in tremor control, radiofrequency thalamotomy may be associated with more complications and neurological adverse effects than deep brain stimulation²⁰; the existing literature estimates a risk of permanent complications following radiofrequency thalamotomy of 13% to 38%.^{23,24} Although deep brain stimulation has been found to be effective in terms of tremor control,^{17,25} as many as half of all people with essential tremor who have undergone the procedure report diminished tremor control 5 years post-surgery,²² and improvements in activities of daily living and quality of life may not be sustained 1 to 7 years following surgery.^{22,26}

A recent systematic review reported that both thalamotomy and deep brain stimulation may produce speech and language difficulties (most frequently hypophonia, dysarthria, and dysphasia), which are two to three times more likely to occur after bilateral than unilateral procedures.²⁷ For people with essential tremor in particular, the risk of language adverse effects has been found to be higher with deep brain stimulation than with radiofrequency thalamotomy.²⁷

The surgical options for a person with no contraindications to surgery are typically considered by weighing the benefits and risks of each procedure, along with the local availability of types of procedure. Deep brain stimulation is now the preferred surgical procedure for people with essential tremor in many jurisdictions, largely replacing radiofrequency thalamotomy.²¹ A further consideration is the willingness of the person to accept aspects of invasive neurosurgical procedures such as craniotomy, general anaesthetic, and permanent, implanted hardware.

Health Technology Under Review

Magnetic resonance-guided focused ultrasound (MRgFUS) is a noninvasive surgical technology with two components: magnetic resonance imaging (MRI) and high-intensity focused ultrasound. In MRgFUS neurosurgery, MRI provides detailed images of the brain in real time during the surgery, allowing for precision in identifying the target area, thus minimizing risk to surrounding tissue.²⁸ The high-intensity focused ultrasound transducer contains 1,024 rays of ultrasound waves, which are emitted to a focal point through the intact skull.²⁸ As the rays are focused and converge, they ablate the target brain tissue.²⁸ Throughout the procedure, ongoing, real-time feedback of thermal data allows the clinical team to precisely adjust the location and temperature parameters.²⁸ During the procedure, the patient is conscious, and the functional

effects of the procedure are clinically assessed throughout. This allows the multidisciplinary clinical team to refine and confirm the correct target and appropriate number of sonications (repetitions of ultrasound beam application).²⁸

With MRgFUS neurosurgery, tremor improvement is immediate, and because the procedure is noninvasive, recovery is quick, and surgical complications such as hemorrhage and infection are minimized.²⁸ Because it is noninvasive, MRgFUS neurosurgery offers a treatment option for people who otherwise have none. This includes people ineligible for the currently available surgical procedures (e.g., elderly people for whom the risks of invasive surgery outweigh the potential benefits), people with surgical contraindications (e.g., those with unstable cardiac disease), and people who find invasive procedures or the associated risks unacceptable.

MRgFUS neurosurgery is inappropriate for people with contraindications to MRI and for the small proportion of people with a skull density that would prevent the therapeutic temperature from being reached.

Regulatory Information

Health Canada approved the use of InSightec's (Tirat Carmel, Israel) Exablate Neuro (also called Exablate 4000) MRgFUS system for the unilateral treatment of idiopathic medication-refractory essential tremor in May 2016 (licence 96969; personal communication, Health Canada, October 11, 2016).

Ontario Context

The Exablate Neuro MRgFUS system is currently available in just two centres in Canada, both in Ontario. At the time of writing, the total capacity to perform MRgFUS neurosurgery was estimated at four patients per month. Local experts advised that current capacity is insufficient to meet the demand of people with essential tremor for whom this surgery is appropriate, owing to limitations on the necessary MRI suite time, as well as financial considerations, as the procedure is presently financed only with research funds. At the time of writing, the Ontario Ministry of Health and Long-Term Care advised that MRgFUS neurosurgery for the treatment of essential tremor is not publicly funded in any province in Canada. However, the N124 billing code in the Ontario *Schedule of Benefits: Physician Services Under the Health Insurance Act* addresses functional stereotactic neurosurgery for physician remuneration of thalamotomy.²⁹

CLINICAL EVIDENCE

Research Question

What are the effectiveness and safety of magnetic resonance-guided focused ultrasound (MRgFUS) neurosurgery for the treatment of moderate to severe, medication-refractory essential tremor?

Methods

We developed the research questions in consultation with people with essential tremor, clinical experts, and other health system stakeholders.

Clinical Literature Search

We performed a literature search on April 11, 2017, to retrieve studies published from inception to the search date. We used the Ovid interface to search the following databases: MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Health Technology Assessment, and National Health Service Economic Evaluation Database (NHSEED).

Medical librarians developed the search strategies using controlled vocabulary (i.e., Medical Subject Headings) and relevant keywords. The final search strategy was peer-reviewed using the PRESS Checklist.³⁰ We created database auto-alerts in MEDLINE and Embase and monitored them for the duration of the health technology assessment review.

We performed targeted grey literature searching of health technology assessment agency websites and clinical trial registries. See Appendix 1 for the literature search strategies, including all search terms.

Literature Screening

A single reviewer used DistillerSR management software to conduct an initial screening of titles and abstracts and obtained the full text of studies that appeared eligible for the review, according to the inclusion criteria. The author then examined the full-text articles and selected studies that were eligible for inclusion. We reported citation flow and primary reason for exclusion of full-text articles according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.³¹

Inclusion Criteria

- English-language full-text publications
- Studies published prior to April 11, 2017
- Randomized controlled trials, systematic reviews, and nonrandomized studies of MRgFUS neurosurgery alone or MRgFUS neurosurgery compared with one or more of the following:
 - Radiofrequency thalamotomy
 - Deep brain stimulation (unilateral or bilateral)
 - Gamma Knife thalamotomy
 - Control intervention (e.g., sham)

Exclusion Criteria

- Animal and in vitro studies
- Feasibility, clinico-radiologic, and technical (e.g., targeting accuracy) studies
- Editorials, case reports, and commentaries
- Conference abstracts and posters
- Studies of people with untreated or mild essential tremor or with a primary presentation of voice, head, or trunk tremor or ataxia
- Studies of people with surgical contraindications (e.g., advanced age, unstable cardiovascular or respiratory disease, inability to communicate) or who have other specific contraindications or clinical or physical features that preclude them from eligibility for receiving MRgFUS neurosurgery (e.g., contraindications to MRI scanning)
- Studies of people with movement disorders other than essential tremor (e.g., Parkinson's disease, Wilson disease, enhanced physiologic tremor)
- Studies including mixed–movement disorder populations that do not analyze data or provide data or results by diagnostic subgroup (i.e., essential tremor alone)
- Studies on medication, superficial brain stimulation, experimental treatments, and surgery

Outcomes of Interest

- Tremor severity and disability assessed by tools such as the following:
 - Versions of the Fahn–Tolosa–Marín (FTM) Clinical Rating Scale for Tremor (e.g., the Clinical Rating Scale for Tremor [CRST])
 - Essential Tremor Rating Assessment Scale (TETRAS)
 - Columbia University Assessment of Disability in Essential Tremor (CADET)
- Quality of life (assessed using a validated tool; e.g., Quality of Life in Essential Tremor [QUEST])
- Activities of daily living (assessed using a validated tool)
- Durability of effect over time
- Adverse effects (i.e., complications and side effects)
- Adverse events

During scoping, we did not detect any potential health inequities related to the effect of MRgFUS neurosurgery for the treatment of essential tremor. We report any relevant equity issues with regard the effect of MRgFUS neurosurgery for the treatment of essential tremor across different populations as defined by the PROGRESS-Plus categories identified during the review process.³²

Data Extraction

A single reviewer extracted relevant information on study context, methods, population, intervention, comparators, outcomes, results, and risk-of-bias items into a data form, based on the information available in the published articles.

Statistical Analysis

We report the results from each included study. We calculated measures of central tendency, confidence intervals, and proportions from the reported data, as needed. We did not perform a

meta-analysis of the results, as we had planned, owing to heterogeneity in study designs, analyses, and outcome measurement across the studies.

Critical Appraisal of Evidence

We assessed risk of bias to evaluate the internal validity of individual studies using the Cochrane Risk of Bias tool for randomized controlled trials³³ and the Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS)³⁴ for nonrandomized studies.

We evaluated the quality of the body of evidence for each outcome according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Handbook.³⁵ The quality reflects our certainty about the evidence. We assessed the body of evidence based on the following considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias.

We could not formally assess publication bias using funnel-plot methodology or statistical methods owing to an insufficient number of studies.

Expert Consultation

Beginning in February 2017, we solicited local expert feedback on the use of MRgFUS neurosurgery for the treatment of medication-refractory essential tremor. We consulted with experts in specialty areas including neurology, neurosurgery, medical physics, and health care administration. The role of the expert advisors was to provide important contextual information on essential tremor, the use of MRgFUS neurosurgery to treat essential tremor, the diffusion of the MRgFUS technology, and clinical issues related to the treatment of Ontarians with essential tremor. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of the consulted experts.

Results

Literature Search

The literature search yielded 706 citations published from inception to April 11, 2017, after removing duplicates. Eight studies reported in ten articles³⁶⁻⁴⁵ (seven nonrandomized studies and one randomized control trial) met the inclusion criteria. We reviewed the reference lists of the included studies but identified no additional citations. We identified one further eligible study published since conducting our systematic literature search, for a total of nine included studies.

Figure 1 presents the PRISMA flow diagram. The characteristics of the included studies are presented in Table 2. Appendix 3 provides a selected list of studies excluded after full-text review that includes the primary reason for exclusion.

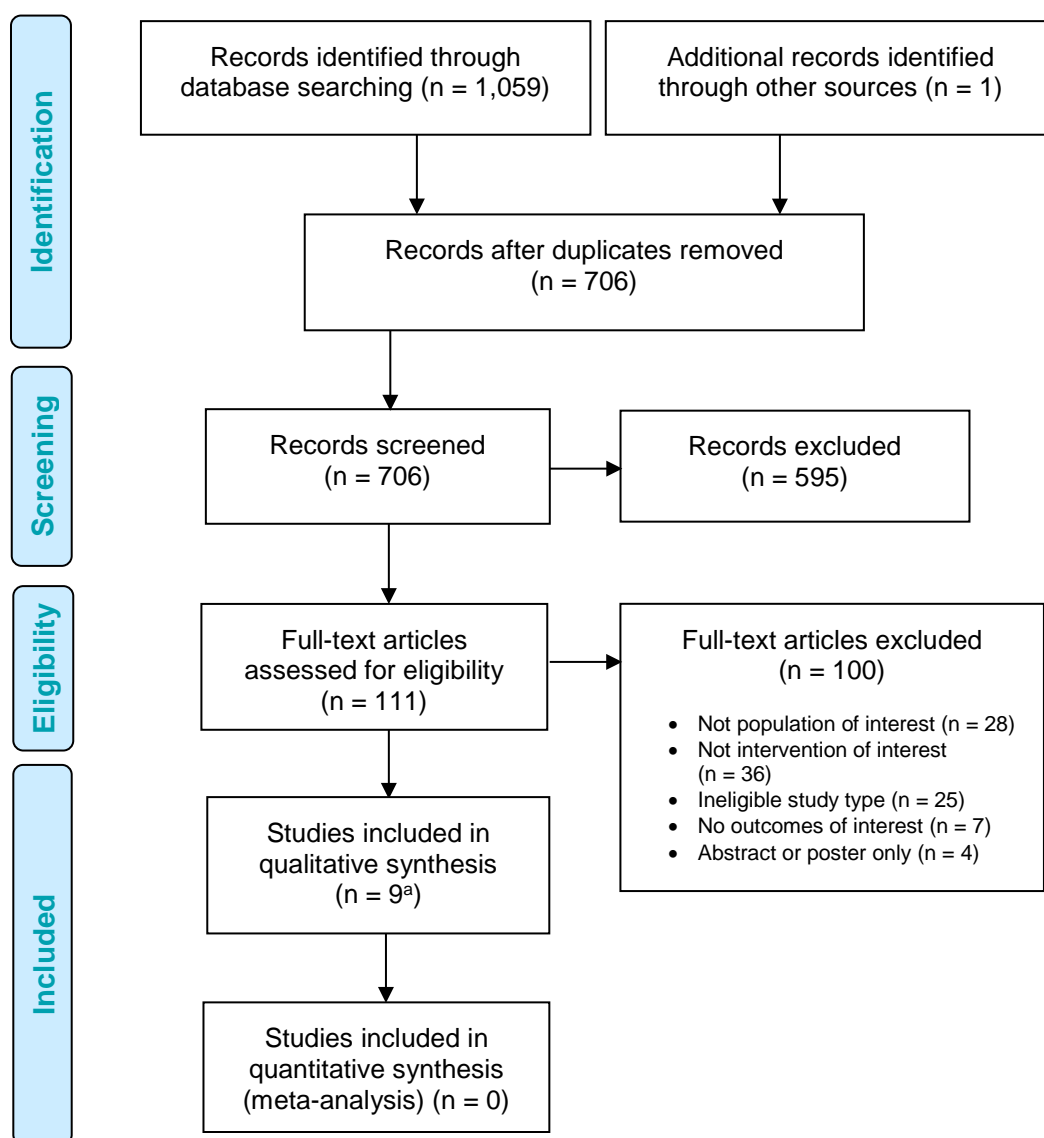


Figure 1: PRISMA Flow Diagram—Clinical Evidence Review

^aNine studies reported in 11 articles.
 Source: Adapted from Moher et al.³¹

Table 2: Characteristics of Included Studies

Author, Year	Country	Study Design	Enrolment Time Frame	N	Intervention(s)	MRgFUS Target	Outcomes of Interest Reported (Time of Evaluation)
Kim et al, 2017 ⁴⁶	Republic of Korea	Retrospective analysis (chart review)	1995–2014	59	MRgFUS DBS RF thalamotomy	VIM	Degree of tremor improvement (1 month, 12 months) Recurrence Side effects/complications
Schreglmann et al, 2017 ⁴²	Switzerland	Prospective, uncontrolled, single-centre, interventional study	NR	6	MRgFUS	CTT	Tremor severity (6 months) QUEST (6 months) Side effects/complications AE
Zaaroor et al, 2017 ⁴⁵	Israel	Single cohort	Nov. 2013–Jan. 2016	18 ^a	MRgFUS	VIM	Tremor severity (1 month, 6 months) QUEST (1 month, 6 months) Recurrence AE
Elias et al, 2016 ³⁸	Canada, Japan, Republic of Korea, United States	Prospective, sham-controlled, multicentre RCT	Aug. 2013–Sep. 2014	76	MRgFUS Sham MRgFUS	VIM	Tremor severity (3 months) QUEST (3 months) Recurrence (12 months) Side effects/complications AE
Gallay et al, 2016 ³⁹	Switzerland	Single cohort	NR	21	MRgFUS	CTT	Tremor severity (12 months) AE
Huss et al, 2016 ⁴⁰	United States	Retrospective analysis (chart review)	Jan. 2004–Jul. 2013	85	MRgFUS DBS	VIM	Tremor severity (pre- vs. post-operative) ^b QUEST (pre- vs. post-operative) ^b Side effects/complications AE
Chang et al, 2015 ³⁶	Republic of Korea	Single cohort	Mar. 2012–Nov. 2012	11	MRgFUS	VIM	Tremor severity (6 months) AE
Elias et al, 2013 ^{37,43,44}	United States	Open-label uncontrolled study (phase I)	Feb. 2011–Dec. 2011	15	MRgFUS	VIM	Tremor severity (3 months, 12 months) QUEST (12 months) Side effects/complications AE

Author, Year	Country	Study Design	Enrolment Time Frame	N	Intervention(s)	MRgFUS Target	Outcomes of Interest Reported (Time of Evaluation)
Lipsman et al, 2013 ⁴¹	Canada	Single cohort	May 2012–Jan. 2013	4	MRgFUS	VIM	Tremor severity (1 month, 3 months) Side effects/complications AE

Abbreviations: AE, adverse events; CTT, cerebellothalamic tract of the posterior thalamic area; DBS, deep brain stimulation; MRgFUS, magnetic resonance-guided focused ultrasound; NR, not reported; QUEST, Quality of Life in Essential Tremor questionnaire; RCT, randomized controlled trial; RF, radiofrequency; VIM, ventral intermediate nucleus of the thalamus.

^aThe study population included people with tremor conditions other than essential tremor (n = 12); some results were reported separately by condition.

^bFor deep brain stimulation, the timing of postoperative measurement varied from 3 to 24 months (mean: 13.1 months) after the device was optimized. For MRgFUS thalamotomy, postoperative measurement occurred at 12 months, except for n = 1, who was assessed at 3 months (mean: 11.8 months).

Tremor Severity

All nine included studies^{36-42,45,46} reported on the impact of MRgFUS neurosurgery on tremor severity. Eight studies assessed severity with either the original FTM scale or its later version, the CRST. Both versions generate an overall score that reflects tremor severity, as well as three subscales that quantify the tremor (part A), action tremor of the upper extremity (part B; assesses tremor during movement via handwriting, drawing, and liquid-pouring tasks), and functional disability in activities of daily living (part C).⁶ For simplicity, we use *CRST* to refer to both versions of the scale throughout and report intra-study results for the version used in each study. The study by Kim and colleagues⁴⁶ did not use CRST, but categorized treatment response according to extent of tremor abolition after surgery. All study participants across studies had moderate to severe, disabling essential tremor upon study enrolment, and of those who underwent MRgFUS neurosurgery, none had contraindications to the procedure. All studies used the Exablate Neuro ultrasound array paired with a compatible 3-Tesla MRI for MRgFUS procedures.

Comparative Studies

MRgFUS Thalamotomy Versus Sham

In the 2016 randomized controlled trial by Elias et al,³⁸ 76 people with essential tremor were randomized in a 3:1 ratio to receive MRgFUS ventral intermediate nucleus thalamotomy or a sham procedure. Upper extremity tremor severity (as measured by parts A and B of the CRST) was assessed via video 3 months postoperatively by a neurologist not involved in patient care or the trial and who was blinded to treatment allocation. The mean age of participants was 71 years (+/- 8.2 years), 75% were of Caucasian ethnicity with most others being Asian, 83% were right-handed, and 68% were male. There were no differences between the two groups in baseline demographic characteristics or tremor severity.³⁸ The primary outcome of upper extremity tremor (Table 3) was analyzed for differences between groups at 3 months, and also for difference from baseline at 3 months and 12 months in the MRgFUS arm.

Table 3: Intention-to-Treat Analysis of Upper Extremity Tremor Severity—MRgFUS Thalamotomy Versus Sham

Time Point	Mean Score (SD)		Mean Improvement vs. Baseline		Mean Difference, Points (95% CI)	P Value
	MRgFUS	Sham	MRgFUS	Sham		
Baseline	18.1 (4.8)	16.0 (4.4)	—	—	—	NS
3 months	9.6 (5.1)	15.8 (4.9)	47%	0.1%	-8.3 (-5.9 to -10.7)	< .001 ^a
12 months	10.9 (4.5)	NA ^b	40%	NA ^b	-7.2 (-6.1 to -8.3)	< .001 ^c

Abbreviations: CI, confident interval; MRgFUS, magnetic resonance-guided focused ultrasound; NA, not applicable; NS, not significant; SD, standard deviation.

Note: Upper extremity tremor severity was assessed via parts A and B of the Clinical Rating Scale for Tremors (CRST), where higher scores indicate greater severity. The maximum possible score is 32.

^aP value is for the between-groups difference at 3 months follow up.

^bAfter the 3-month blinded period, sham participants could cross over to receive MRgFUS thalamotomy.

^cP value is for the change from baseline within the MRgFUS thalamotomy group.

Source: Elias et al, 2016.³⁸

Three months after the procedure, people who had undergone MRgFUS thalamotomy experienced a 47% improvement in upper extremity tremor; this result was statistically significant compared with both their baseline severity ($P < .001$) and with the 0.1% improvement seen in the sham group over the same time frame ($P < .001$).³⁸ This result translated to an absolute mean change in score at 3 months between the MRgFUS and sham groups of -8.3 points (95% confidence interval [CI]: 5.9–10.7, $P < .001$).

The authors also analyzed change in tremor severity from baseline within each group. In the MRgFUS group, upper extremity tremor severity scores were significantly reduced (i.e., tremor improved) at 1 month, 3 months, 6 months, and 12 months following treatment ($P < .001$).³⁸ There was no change from baseline scores in the sham group.³⁸

Total CRST scores were analyzed similarly post hoc; Table 4 presents these results. The mean total CRST tremor score (based on scores from parts A, B, and C) for participants at baseline was 49.5, out of a possible 152, with no difference between groups.³⁸

Table 4: Post-hoc Analysis of Overall Tremor Severity—MRgFUS Thalamotomy Versus Sham

Time Point	Mean Score (SD)		Mean Improvement vs. Baseline		Mean Difference, Points (95% CI)	P Value
	MRgFUS	Sham	MRgFUS	Sham		
Baseline	50.1 (14.0)	44.1 (12.7)	—	—	—	NS
3 months	29.6 (13.0)	43.1 (13.1)	41%	2%	NR	< .001 ^a
12 months	32.4 (14.5)	NA ^b	35%	NA ^b	NR	NA

Abbreviations: CI, confident interval; MRgFUS, magnetic resonance-guided focused ultrasound; NA, not applicable; NS, not significant; SD, standard deviation.

Note: Overall tremor severity was assessed via parts A, B, and C of the Clinical Rating Scale for Tremors (CRST), where higher scores indicate greater tremor severity. The maximum possible score is 152.

^aP value is for the between-groups difference at 3 months follow up.

^bAfter the 3-month blinded period, sham participants could cross over to receive MRgFUS thalamotomy. Only the within-group differences from baseline for the MRgFUS thalamotomy group was reported for the 12-month time point.

Source: *Elias et al, 2016.*³⁸

At 3 months post-procedure, those in the MRgFUS group experienced a statistically significant 41% improvement in total tremor, compared with 2% in the sham group ($P < .001$; Figure 2).³⁸ In the MRgFUS group, 27 patients (48%) experienced an improvement in tremor severity of more than 50%, 24 (43%) experienced a change of between 10% and 50%, and 5 (9%) experienced an improvement of less than 10%.³⁸ The tremor improvement seen at 3 months in the MRgFUS group was sustained at 1 year (35%). No P values for change from baseline were reported.

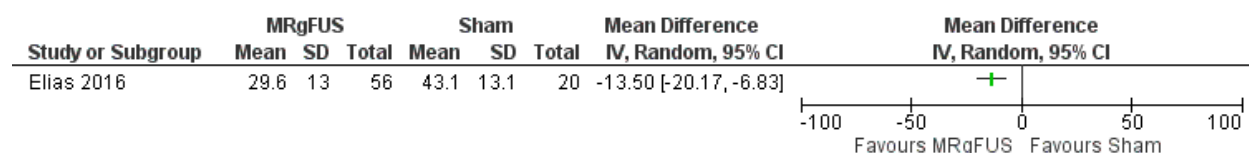


Figure 2: CRST Scores at 3 Months Post-surgery—MRgFUS Thalamotomy Versus Sham (Post-hoc Analysis)

Source: *Elias et al, 2016.*³⁸

Unblinded Cohort of Randomized Controlled Trial

In the 2016 randomized controlled trial by Elias et al,³⁸ participants allocated to the sham arm were permitted to cross over to receive MRgFUS thalamotomy after 3 months and were then followed, with their outcomes analyzed in the same blinded manner as the MRgFUS group. Of those in the sham group, 19 of 20 participants crossed over, and two participants from the MRgFUS group in whom the procedure was incomplete (therapeutic temperature was not reached in the initial procedure) underwent MRgFUS thalamotomy.³⁸ Three months postoperatively, upper extremity tremor improved significantly by 55% compared with baseline (16.5 +/- 4.2 to 7.4 +/- 3.9, $P < .001$).³⁸ At 6 months, there was a statistically significant 52% improvement in upper extremity tremor compared with baseline (8.0 +/- 3.9, $P < .001$).³⁸ Participants' overall tremor severity also significantly improved between baseline and 1 month, 3 months, 6 months, and 12 months ($P < .001$ for all).³⁸

MRgFUS Thalamotomy Versus Deep Brain Stimulation

Huss et al⁴⁰ conducted a retrospective analysis of people with essential tremor treated with either MRgFUS thalamotomy ($n = 15$) or deep brain stimulation (unilateral or bilateral, $n = 70$) at one U.S. centre. This was done by reviewing the charts of patients with essential tremor who had been treated with these neurosurgeries over a period of approximately a decade. The authors compared patients' functional and quality-of-life outcomes both within and between groups. The authors analyzed outcomes for patients treated by one neurosurgeon between January 2004 and July 2013 who had completed both pre- and postoperative CRST and QUEST assessments. The groups were two-thirds male, with mean ages ranging from 63.5 to 71.7 years.⁴⁰

At baseline, patients who had received MRgFUS thalamotomy had significantly lower overall CRST scores and tremor scores than patients who had received bilateral deep brain stimulation ($P < .05$ for both).⁴⁰ No differences were seen in either task performance or dominant-hand subscores between groups. Importantly, the authors found some evidence that patients with marked tremor in the midline of the body may have been more likely to undergo bilateral deep brain stimulation than MRgFUS thalamotomy, as they scored significantly higher on axial tremor scores than patients in the MRgFUS group ($P < .05$).⁴⁰

Regardless of treatment, patients with essential tremor experienced significant improvement postoperatively in total CRST score, tremor score, functional tasks, and disability compared with baseline ($P < .05$).⁴⁰ Improvements in total CRST score were 79.5% for those who underwent bilateral deep brain stimulation, 62.8% for those who underwent unilateral deep brain stimulation, and 55.7% for those who underwent MRgFUS thalamotomy.⁴⁰ The upper-extremity tremor of all patients improved significantly after treatment, regardless of surgery type ($P < .05$).⁴⁰ However, no significant change in axial tremor was seen in the postoperative observation of patients who received MRgFUS thalamotomy (14.8%, $P = .52$), in contrast to the significant improvement seen with both unilateral and bilateral deep brain stimulation ($P < .05$ for all).⁴⁰ Bilateral deep brain stimulation yielded lower scores on part B of the CRST (tremor during tasks) than MRgFUS thalamotomy ($P < .05$), indicating greater improvement.⁴⁰

Kim et al⁴⁶ also conducted a retrospective analysis of people with medication-refractory essential tremor who had undergone unilateral MRgFUS thalamotomy ($n = 23$), unilateral deep brain stimulation ($n = 19$), or unilateral radiofrequency thalamotomy ($n = 17$) at their medical centre in Seoul, Korea, over about 20 years. The study groups had median ages of between 63 and 66 years (interquartile ranges varied from 26 to 73 years). The MRgFUS thalamotomy

group was 87% male, the deep brain stimulation group was 68% male, and the radiofrequency thalamotomy group was 53% male.⁴⁶

Tremor improvement was measured on a different disease-specific scale than the CRST, as the CRST was unavailable for the radiofrequency thalamotomy group. The authors categorized symptoms as absent (100% tremor abolition), occasional (> 90% abolition), partial improvement (> 50% abolition), or showing no improvement (< 50% improvement).⁴⁶ The results were then dichotomized as either success (absent or occasional tremor) or failure (partial or no improvement). It is important to note that this high threshold for success (> 90% tremor abatement) would have led to a conservative estimate of effectiveness. The authors analyzed their data using a generalized estimating equation model to compare outcomes between the three groups.

Tremor severity improved significantly from baseline in all groups at both 1 month and 12 months postoperatively ($P < .001$ and $P < .0001$, respectively).⁴⁶ The model found no significant differences between the three groups in either treatment success ($P = .54$ at 1 month; $P = .62$ at 12 months) or rate of complete remission (i.e., 100% abolition) at 1 month ($P = .14$) or 12 months of follow-up ($P = .62$).⁴⁶ The proportion of treatment success for MRgFUS thalamotomy compared with deep brain stimulation, and for MRgFUS thalamotomy compared with radiofrequency thalamotomy, respectively, are described separately in the paragraphs that follow. We calculated 95% confidence intervals for the proportions of success and remission rates for each group.

MRgFUS thalamotomy resulted in an improvement of more than 90% in 91.3% of patients at the 1 month follow-up (95% CI: 79.8–100%), and in 78.3% of patients (95% CI: 66.8–89.8%) at the 12-month follow-up.⁴⁶ Among patients who had undergone deep brain stimulation, 89.5% experienced treatment success (i.e., > 90% improvement) at 1 month (95% CI: 75.7–100%), and 84.2% experienced treatment success at 12 months (95% CI: 67.8–100%).

At 1 month, 43.5% (95% CI: 23.2–63.8%) of patients who had undergone MRgFUS thalamotomy experienced complete tremor abolition, compared with 31.6% (95% CI: 10.7–52.5%) of those who had undergone deep brain stimulation. At 12 months, 34.8% (95% CI: 15.3–54.2%) of patients who had undergone MRgFUS thalamotomy experienced complete tremor abolition, compared with 47.4% (95% CI: 24.9–69.9%) of patients who had undergone deep brain stimulation.

MRgFUS Thalamotomy Versus Radiofrequency Thalamotomy

In the study by Kim and colleagues,⁴⁶ the authors compared MRgFUS thalamotomy with radiofrequency thalamotomy and deep brain stimulation in terms of tremor control and complications.⁴⁶ The generalized estimating equation model found no significant differences between the three groups with regard to treatment success or remission at any time point.⁴⁶ Using the categorization of either success (complete or > 90% tremor abolishment) or failure (< 90% tremor improvement) described above, MRgFUS thalamotomy was successful in 91.3% of patients at 1 month follow-up (95% CI: 79.8–100%) and in 78.3% (95% CI: 66.8–89.8%) of patients at 12 months follow-up. Radiofrequency thalamotomy was successful in 100% (95% CI: 78.3–100%) of patients at 1 month and in 70.6% (95% CI: 48.9–92.3%) of patients at 12 months.

At 1 month, 43.5% (95% CI: 23.2–63.8%) of patients who had undergone MRgFUS thalamotomy and 76.5% (95% CI: 56.3–95.7%) of patients who had undergone radiofrequency

thalamotomy experienced complete tremor abolition.⁴⁶ At 12 months, 34.8% (95% CI: 15.3–54.2%) of patients in the MRgFUS group and 29.4% (95% CI: 25.7–51.1%) of patients in the radiofrequency group experienced complete tremor abolishment.

Noncomparative Cohort Studies

Six studies^{36,37,39,41,42,45} examined the impact of MRgFUS neurosurgery (ventral intermediate nucleus thalamotomy or cerebellothalamic tractotomy) in cohorts of people with essential tremor. Table 5 summarizes the characteristics of these cohorts.

Table 5: Participant Characteristics in Cohort Studies of MRgFUS Neurosurgery

Author, Year	N	Mean Age, Years (SD)	Age Range, Years	% Male
Schreglmann et al, 2017 ⁴²	6	70.7 (8.5)	58–82	33
Zaaroor et al, 2017 ⁴⁵	18 ^a	73.1 (6.2)	64–87	67
Gallay et al, 2016 ³⁹	21	69.1 (9.2)	NR	71
Chang et al, 2015 ³⁶	11	64.8 (7.71)	53–78	82
Elias et al, 2013 ^{37,43,44}	15	66.6 (8)	53–79	67
Lipsman et al, 2013 ⁴¹	4	70.8 (NR)	58–77	100

Abbreviations: MRgFUS, magnetic resonance-guided focused ultrasound; NR, not reported; SD, standard deviation.

^aThere were 30 study participants, of whom 18 had essential tremor and 12 had either Parkinson's disease or tremor-dominant Parkinson's disease. The characteristics described reflect means, ranges, and proportions for the subset of participants with essential tremor.⁴⁵

Sample sizes of participants with essential tremor ranged from 4 to 21, with mean ages in the mid- to late 60s. The authors analyzed total or subscale CRST scores after MRgFUS treatment to determine the effect of treatment on tremor severity and disability. Follow-up timing ranged from 1 month to 1 year. Table 6 presents the findings of these studies.

Table 6: Improvement in Tremor Severity Observed in Cohort Studies of MRgFUS Neurosurgery

Author, Year	N	CRST Scale(s) Assessed	Baseline Score, Mean (SD)	Follow-Up	Post-treatment Score, Mean (SD)	Improvement	P Value
Ventral Intermediate Nucleus Thalamotomy							
Zaaroor et al, 2017 ⁴⁵	18 ^a	Total	40.7 (11.6)	1 mo	9.3 (7.1)	77%	< .001
				6 mo	8.2 (5.0)	80%	< .001
Chang et al, 2015 ³⁶	11 ^b	Part A	5.1	6 mo	1.4	73%	NR
		Part B	13.0	6 mo	2.6	80%	NR
		Part C	13.5	6 mo	2.8	79%	NR
Elias et al, 2013 ^{37,43,44}	15	Part A	20.4 (5.2)	3 mo	4.3 (3.5)	79%	NR
				12 mo	5.2 (4.8)	75%	.001
		Total	54.9 (14.4)	12 mo	24.3 (14.8)	56%	.001
Lipsman et al, 2013 ⁴¹	4	Part A	21.5 (11.2)	1 mo	7.3 (2.2)	66%	NR
		Part B	28.5 (6.5)	1 mo	16 (7.6)	45.5%	NR
		Part C	20.8 (4.5)	1 mo	8 (4.2)	62%	NR
		Total	70.8 (19.7)	1 mo	31.3 (15.0)	56%	NR
		Part A		3 mo	7.8 (4.6)	65%	NR
		Part B		3 mo	17.3 (6.6)	39.6%	NR
		Part C		3 mo	10.3 (3.3)	50%	NR
		Total		3 mo	35.3 (11.0)	50%	NR
Cerebellothalamic Tractotomy							
Schreglmann et al, 2017 ⁴²	6	Total CRST	43.8 (9.8)	6 mo	19.8 (6.8)	−24 points (95% CI: −18.1 to −29.9)	< .001
		Unilateral (treated side)	14.3 (4.9)	6 mo	2.5 (2.6)	−11.8 points (95% CI: −8.4 to −15.2)	< .001
		Speaking and working	13.8 (3.4)	6 mo	2.5 (0.8)	−11.3 (95% CI: −8.8 to −13.9)	< .001
		Drawing and pouring	8.7 (2.7)	6 mo	2.3 (2.3)	−6.3 (95% CI: −3.8 to −8.9)	< .001

Author, Year	N	CRST Subscale(s) Assessed	Baseline Score, Mean (SD)	Follow-Up	Post-treatment Score, Mean (SD)	Improvement	P Value
Cerebellothalamic Tractotomy							
Gallay et al, 2016 ³⁹	21 ^c	Total	57.6 (13.2)	12 mo	25.8 (17.6)	55%	NR
		Hand function, targeted hand only	12.4 (1.3)	3 mo 12 mo	NR NR	74% 78%	NR NR
Subgroup 1 (Severe)	7	Hand function, targeted hand only	15.3 (1.3)	3 mo 12 mo	NR NR	41% 40%	NR NR
Subgroup 2	14	Hand function, targeted hand only	11.0 (3.3)	3 mo 12 mo	NR NR	92% 90%	NR NR

Abbreviations: CI, confident interval; MRgFUS, magnetic resonance-guided focused ultrasound; NR, not reported; SD, standard deviation.

Note: Essential tremor severity was assessed via the Clinical Rating Scale for Tremor (CRST).

^aThere were 30 study participants, of whom 18 had essential tremor and 12 had either Parkinson's disease or tremor-dominant Parkinson's disease. The characteristics described reflect means, ranges, and proportions for the subset of participants with essential tremor.⁴⁵

^bThere were outcome data for 8 of 11 participants at follow-up.

^cThere were outcome data for 10 of 21 participants at the 12-month follow-up.

In all six studies, tremor improved markedly following treatment compared with baseline.^{36,37,39,41,42,45} Three studies reported that the improvements were statistically significant ($P < .001$ for all),^{37,42,45} whereas the others did not report P values for the comparison.^{36,39,41} Across studies, total CRST scores improved by 50% to 77%; tremor subscale (part A) scores improved by 66% to 83%; task subscale (part B) scores improved by more than 40%; and functional disability subscale (part C) scores improved by 50% or more.^{36,37,39,41,42,45}

In the study of MRgFUS cerebellothalamic tractotomy by Gallay et al,³⁹ participants self-reported that they perceived a 77% improvement in tremor at 1 year post-procedure. Two participants underwent staged bilateral cerebellothalamic tractotomy, involving two procedures performed 1 year apart. One year after the second surgery, these participants reported an improvement of 75% to 88% in their dominant hand and an improvement of 56% to 78% in their nondominant hand.³⁹

Gallay et al³⁹ found that their sample differed in terms of baseline severity measured on the CRST and therefore conducted separate subgroup analyses of participants whose essential tremor was more severe ($n = 7$) versus moderate ($n = 21$). Those in the moderate group experienced greater improvement following surgery than did those in the severe group at 3 months (92% vs. 41%), and these within-group improvements persisted to 1 year.³⁹ However, no statistics were reported for the subgroup comparisons.

Table 7 provides the GRADE assessment of our certainty in this body of evidence.

Table 7: GRADE Evidence Profile for Tremor Severity After MRgFUS Neurosurgery

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Compared With Sham							
1 (RCT) ³⁸	No serious limitations	No serious limitations ^a	No serious limitations	No serious limitations ^b	Undetected ^a	NA	⊕⊕⊕⊕ High
Compared With Deep Brain Stimulation							
2 (Observational) ^{40,46}	Serious limitations (–1) ^c	No serious limitations	No serious limitations	Serious limitations (–1) ^d	Undetected ^a	NA	⊕ Very Low
Compared With Radiofrequency Thalamotomy							
1 (Observational) ⁴⁶	Serious limitations (–1) ^c	No serious limitations ^a	No serious limitations	No serious limitations	Undetected ^a	NA	⊕ Very Low
MRgFUS Only							
6 (Observational) ^{36,37,39,41,42,45}	No serious limitations ^e	No serious limitations ^f	No serious limitations	No serious limitations ^g	Undetected ^h	NA	⊕⊕ Low

Abbreviations: MRgFUS, magnetic resonance-guided focused ultrasound; NA, not applicable; RCT, randomized controlled trial.

^aCannot definitively assess presence or absence because the evidence is derived from a single study.

^bStudy adequately powered, confidence interval for absolute difference in severity scores relatively narrow, mean difference and upper and lower bounds are clinically meaningful, as is relative improvement.

^cRisk of bias was highest owing to retrospective data collection methods. The full risk-of-bias assessment is presented in Appendix 2, Table A2.

^dConsiderable imbalance in group sizes for comparisons, optimal information size criteria not met, and no measures of variance or confidence intervals provided; therefore, uncertainty remains in the precision of estimates.

^eRisk of bias overall judged to be low or unclear for most studies; one study (Zaaroor et al⁴⁵) judged to be at high risk of bias resulting from participant selection. The full risk-of-bias assessment is presented in Appendix 2, Table A2.

^fVariability in exact magnitude of effect, but of questionable importance as all estimates indicate clinically meaningful benefit.

^gSome studies did not meet optimal information size criterion, yet found both statistically significant and clinically meaningful results that are on the same side of the clinical decision threshold.

^hInadequate information reported from studies to formally assess using funnel plot or statistical tests; however, the studies vary in terms of sample size and are generally small.

Functional Disability in Activities of Daily Living

Three studies provided a separate analysis of disability in people with essential tremor receiving MRgFUS thalamotomy.^{37,38,40} As a secondary outcome, functional disability in activities of daily living (assessed via part C of the CRST) was analyzed before and after either MRgFUS thalamotomy or a sham procedure in the 2016 randomized controlled trial by Elias et al.³⁸ At baseline, the greatest degree of disability was observed in drinking and writing.³⁸ Table 8 presents the results from this study.

Table 8: Reduction in Functional Disability—MRgFUS Thalamotomy Versus Sham

Time Point	Mean Score (SD)		Mean Improvement vs. Baseline		P Value
	MRgFUS	Sham	MRgFUS	Sham	
Baseline	16.5 (4.6)	16.0 (4.3)	–	–	NS
3 months	6.2 (5.6)	15.6 (4.6)	62%	3%	< .001 ^a
12 months	6.3 (6.2)	NA ^b	62%	NA ^b	NA

Abbreviations: MRgFUS, magnetic resonance-guided focused ultrasound; NA, not applicable; NS, not significant; SD, standard deviation.

Note: Functional disability was assessed via part C of the Clinical Rating Scale for Tremors (CRST), where higher scores indicate greater severity. The maximum possible score is 32.

^aP value is for the between-groups difference at 3 months follow up.

^bAfter the 3-month blinded period, sham participants could cross over to receive MRgFUS thalamotomy. Only the within-group difference from baseline for the MRgFUS thalamotomy group was reported for the 12-month time point.

Source: Elias et al, 2016.³⁸

A significant reduction was seen in functional disability in the MRgFUS group compared with sham ($P < .001$).³⁸ By 12 months follow-up, participants who had received MRgFUS thalamotomy experienced improvement in every activity to the level of either normal (score: 0) or mild disability (score: 1), with the exception of writing (mean score: 1.21 \pm 1.14).³⁸

In their retrospective study, Huss et al⁴⁰ analyzed reduction in disability (assessed via part C of the CRST) in people with essential tremor who had undergone unilateral or bilateral deep brain stimulation versus MRgFUS thalamotomy, as well as within each group compared with baseline. Although a statistically significant postoperative improvement ($P < .05$) was seen in all groups, no significant differences in improvement were found between those who had undergone bilateral deep brain stimulation versus MRgFUS thalamotomy ($P = .59$), or between those who had undergone unilateral versus bilateral deep brain stimulation ($P = .42$).⁴⁰

In their 2013 cohort study, Elias et al³⁷ found a statistically significant improvement in disability from baseline to 12 months following MRgFUS thalamotomy (18.2 \pm 4.1 vs. 2.8 \pm 3.4, $P < .001$). This result corresponds to an 85% improvement postoperatively.³⁷

Table 9 summarizes the disability outcome results for the studies by Huss et al⁴⁰ and Elias et al.^{37,43,44} Table 10 provides the GRADE assessment of the body of evidence from these studies.

Table 9: Reduction in Functional Disability Observed in Nonrandomized Studies of MRgFUS Thalamotomy

Author, Year (Study Design)	N	Intervention	Baseline Score, Mean (SD)	Follow- Up	Post-treatment Score, Mean (SD)	Improvement	P Value, Change From Baseline
Huss et al, 2015 ⁴⁰ (Retrospective analysis)	15	MRgFUS	18.2	NR	2.8	85.4%	< .05 ^a
	13	Unilateral DBS	18.9		3.2	88.4%	< .05 ^a
	57	Bilateral DBS	19.9		2.3	83.1%	< .05 ^a
Elias et al, 2013 ^{37,43,44} (Cohort)	15	MRgFUS	18.2 (4.1)	12 mo	2.8 (3.4)	85%	< .001

Abbreviations: DBS, deep brain stimulation; MRgFUS, magnetic resonance-guided focused ultrasound; NR, not reported; SD, standard deviation.

Note: Disability was assessed via part C of the Clinical Rating Scale for Tremors (CRST), where higher scores indicate greater severity. The maximum possible score is 32.

^aP values presented reflect change from baseline. In the study by Huss et al,⁴⁰ the between-groups comparisons for degree of reduction in disability were not significant for the comparison of bilateral deep brain stimulation with either unilateral deep brain stimulation ($P = .42$) or MRgFUS thalamotomy ($P = .59$).

Table 10: GRADE Evidence Profile for Functional Disability After MRgFUS Thalamotomy

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Compared With Sham							
1 (RCT) ³⁸	No serious limitations	No serious limitations ^a	No serious limitations	No serious limitations ^b	Undetected ^a	NA	⊕⊕⊕⊕ High
Compared With Deep Brain Stimulation							
1 (Observational) ⁴⁰	Serious limitations (–1) ^c	No serious limitations ^a	No serious limitations	Serious limitations (–1) ^d	Undetected ^a	NA	⊕ Very Low
MRgFUS Only							
1 (Observational) ³⁷	No serious limitations ^e	No serious limitations ^a	No serious limitations	No serious limitations ^f	Undetected ^a	NA	⊕⊕ Low

Abbreviations: MRgFUS, magnetic resonance-guided focused ultrasound; NA, not applicable; RCT, randomized controlled trial.

^aCannot definitively assess presence or absence because evidence is derived from a single study.

^bStudy adequately powered; absolute change and relative improvement are both clinically meaningful and statistically significant.

^cRisk of bias was highest owing to retrospective data collection methods. The full risk-of-bias assessment is presented in Appendix 2, Table A2.

^dConsiderable imbalance in group sizes for comparisons, optimal information size criteria not met, no measures of variance or confidence intervals provided; therefore, uncertainty remains in precision of estimates.

^eRisk of bias judged to be low for all considerations except participant selection, which was unclear. The full risk-of-bias assessment is presented in Appendix 2, Table A2.

^fConfidence interval for absolute difference in severity scores relatively narrow, mean difference and upper and lower bounds are clinically meaningful, as is relative improvement.

Tremor Recurrence

Two studies reported on the recurrence of tremor in people treated with MRgFUS thalamotomy separately from the stability of tremor improvement over time.^{45,46} In the study by Zaaroor et al,⁴⁵ two patients (11%) experienced some tremor recurrence within the 6 months post-surgery, although tremor severity was less disabling than at baseline. In one case, tremor recurred after 3 weeks but was less debilitating than at baseline. In the other case, tremor recurred after 3 months but appeared only during writing, whereas at baseline the tremor precluded all activities.⁴⁵

The retrospective study by Kim et al⁴⁶ reported tremor recurrence, defined as return to baseline tremor severity, in each of three groups: people who had undergone MRgFUS thalamotomy, deep brain stimulation, or radiofrequency thalamotomy. Twelve months after surgery, one participant who had undergone MRgFUS thalamotomy (4.3%), one who had undergone deep brain stimulation (5.2%), and three who had undergone radiofrequency thalamotomy (17.6%) experienced tremor recurrence.⁴⁶

Table 11 provides the GRADE assessment of the body of evidence for the outcome of tremor recurrence.

Table 11: GRADE Evidence Profile for Tremor Recurrence After MRgFUS Neurosurgery

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
MRgFUS Only							
2 (Observational) ^{45,46}	Serious limitations (–1) ^a	No serious limitations	No serious limitations	No serious limitations ^b	Undetected	NA	⊕ Very Low

Abbreviations: MRgFUS, magnetic resonance-guided focused ultrasound; NA, not applicable.

^aJudged to be at high risk of selection bias owing to participants being offered a choice between two surgeries and choosing MRgFUS neurosurgery in one study,⁴⁵ and retrospective data collection in the other.⁴⁶ The full risk-of-bias assessment is presented in Appendix 2, Table A2.

Quality of Life

Participants' self-reported quality of life was measured with the Quality of Life in Essential Tremor (QUEST) questionnaire in five studies.^{37,38,40,42,45} The QUEST questionnaire captures several aspects of quality of life, including communication, work and finances, hobbies and leisure, physical activities of daily living, and psychosocial well-being.⁴⁷ Higher scores reflect poorer quality of life.

In their 2016 randomized controlled trial, Elias et al³⁸ compared differences in QUEST scores at 3 months after the procedure between the MRgFUS thalamotomy and sham groups. Within the MRgFUS group, the authors also assessed change in quality of life between baseline and 12 months following surgery. Table 12 summarizes these results.

Table 12: Impact on Quality of Life—MRgFUS Thalamotomy Versus Sham

Time Point	Mean Score (SD)		Mean Improvement vs. Baseline		P Value
	MRgFUS	Sham	MRgFUS	Sham	
Baseline	42.6 (18.3)	42.8 (19.5)	—	—	NS
3 months	23.1 (16.9)	41.4 (19.4)	46%	3%	< .001 ^a
12 months	21.7 (17.2)	NA ^b	49%	NA ^b	NA

Abbreviations: MRgFUS, magnetic resonance-guided focused ultrasound; NA, not applicable; NS, not significant; SD, standard deviation.

Note: Quality of life assessed via the Quality of Life in Essential Tremor (QUEST) questionnaire.

^aP value is for the between-groups difference at 3 months follow up.

^bAfter the 3-month blinded period, sham participants could cross over to receive MRgFUS thalamotomy. Only the within-group difference for the MRgFUS thalamotomy group was reported for the 12-month time point.

Source: Elias et al, 2016.³⁸

The authors found that quality of life improved significantly more in the MRgFUS group than in the sham group (46% vs. 3%, $P < .001$).³⁸ For participants treated with MRgFUS thalamotomy, the improvement was sustained at 12-months post-procedure. The largest change from baseline was observed in psychosocial well-being.³⁸ Figure 3 illustrates the mean difference in QUEST scores at 3 month follow-up between the MRgFUS and sham groups.

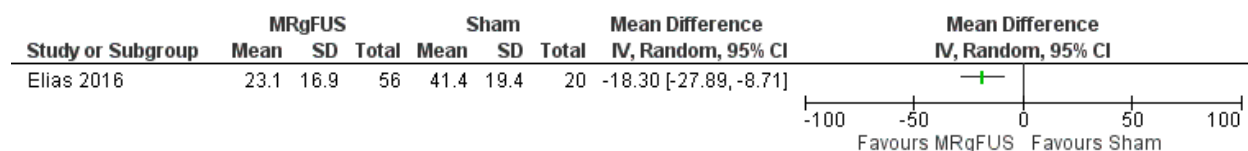


Figure 3: Mean Difference in QUEST Scores at 3 Months—MRgFUS Thalamotomy Versus Sham

Source: Elias et al, 2016.³⁸

In their retrospective study, Huss et al⁴⁰ compared QUEST scores only for participants who had undergone MRgFUS neurosurgery or bilateral deep brain stimulation; QUEST scores were not available for participants who had undergone unilateral deep brain stimulation. After surgery, both the MRgFUS and bilateral deep brain stimulation groups experienced significant improvements in overall quality of life compared with preoperative assessments: MRgFUS participants improved by 68.0%, and bilateral deep brain stimulation participants improved by 72.0% ($P < .05$ for both). However, participants who had undergone MRgFUS thalamotomy did not experience a significant change from baseline in the communication subdomain. No

significant between-groups differences were observed postoperatively in any of the QUEST subdomains.⁴⁰

Caution must be exercised when interpreting the between-groups comparisons, as there were significant between-groups differences at baseline in age and tremor severity. Participants who underwent bilateral deep brain stimulation were older and had more severe tremor than participants in the other groups. Bilateral deep brain stimulation recipients also experienced significantly worse preoperative total quality of life than those who received MRgFUS thalamotomy (QUEST scores of 52.1 vs. 37.5, $P = .009$).⁴⁰ Further, participants who underwent bilateral deep brain stimulation experienced significantly higher dysfunction in the communication and psychosocial subdomains of QUEST preoperatively than patients who underwent MRgFUS ($P < .05$ for both).⁴⁰

Two cohort studies of MRgFUS ventral intermediate nucleus thalamotomy^{37,45} and one of cerebellothalamic tractotomy⁴² found statistically significant and clinically meaningful improvements in quality of life at various time points after MRgFUS neurosurgery.

As shown in Table 13, quality of life improved significantly after MRgFUS neurosurgery in all studies ($P < .05$ for all).^{37,42,45} The significant improvement was observed at 1 month, 6 months, and 12 months post-procedure.^{37,42,45}

Table 13: Improvement in Quality of Life Observed in Cohort Studies of MRgFUS Neurosurgery

Author, Year	N	Target	Baseline, Mean Score (SD)	Follow-Up	Post-treatment, Mean Score (SD)	Improvement	P Value
Zaaroor et al, 2017 ⁴⁵	18 ^a	VIM	44.8 (12.9)	1 mo	13.1 (12.3)	71%	< .001
				6 mo	12.3 (7.2)	73%	< .001
Schreglmann et al, 2017 ⁴²	6	CTT	50.5 (19.4)	6 mo	24.8 (11.4)	52%	.046
Elias et al, 2013 ^{37,43,44}	15	VIM	37 (NR)	12 mo	12 (NR)	68%	.001

Abbreviations: CTT, cerebellothalamic tract; MRgFUS, magnetic resonance-guided focused ultrasound; NR, not reported; SD, standard deviation; VIM, ventral intermediate nucleus of the thalamus.

Note: Quality of life was assessed via the Quality of Life in Essential Tremor (QUEST) questionnaire.

^aThere were 30 study participants, of whom 18 had essential tremor and 12 had either Parkinson's disease or tremor-dominant Parkinson's disease. The characteristics described reflect means, ranges, and proportions for the subset of participants with essential tremor.⁴⁵

Table 14 provides the GRADE assessment of the body of evidence for quality of life after MRgFUS neurosurgery.

Table 14: GRADE Evidence Profile for Quality of Life After MRgFUS Neurosurgery

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Compared With Sham							
1 (RCT) ³⁸	No serious limitations	No serious limitations ^a	No serious limitations	No serious limitations ^b	Undetected ^a	NA	⊕⊕⊕⊕ High
Compared With Deep Brain Stimulation							
1 (Observational) ⁴⁰	Serious limitations (–1) ^c	No serious limitations ^a	No serious limitations	Serious limitations (–1) ^d	Undetected ^a	NA	⊕ Very Low
MRgFUS Only							
3 (Observational) ^{37,42,45}	No serious limitations ^e	No serious limitations ^a	No serious limitations	No serious limitations ^f	Undetected ^a	NA	⊕⊕ Low

Abbreviations: MRgFUS, magnetic resonance-guided focused ultrasound; NA, not applicable; RCT, randomized controlled trial.

^aCannot definitively assess presence or absence because the evidence is derived from a single study.

^bAbsolute change and relative improvement are both clinically meaningful and statistically significant.

^cRisk of bias was highest owing to retrospective data collection methods. The full risk-of-bias assessment is presented in Appendix 2, Table A2.

^dConsiderable imbalance in group sizes for comparisons, optimal information size criteria not met, no measures of variance or confidence intervals provided; therefore, uncertainty remains in the precision of estimates.

^eRisk of bias judged to be low for all considerations except participant selection, which was unclear. The full risk-of-bias assessment is presented in Appendix 2, Table A2.

^fStatistical power an issue in one study; however, a clinically meaningful and statistically significant, large effect was found.

Adverse Effects

MRgFUS Neurosurgery

As reported in four studies, the most frequent sensations and events experienced during the MRgFUS procedure were vestibular symptoms such as dizziness, vertigo, nausea, and vomiting.^{36,37,41,42} In these studies, all symptoms resolved once the sonications were stopped. The frequency and nature of these procedure-related adverse effects were reported as follows:

- Chang et al³⁶: Five of 11 participants experienced vestibular symptoms during sonications (e.g., dizziness, nausea, vomiting). No statically significant difference was observed in the duration of the procedure between participants who did and did not experience symptoms ($P = .361$)
- Elias et al³⁷: Vestibular symptoms experienced during sonications among the 15 participants included one episode of syncope, nine occurrences of head pain, and four instances of a warm or flushed feeling
- Lipsman et al⁴¹: One of four participants experienced paresthesia during sonications, which resolved once the sonications were stopped
- Schreglmann et al⁴²: Four of six participants who underwent cerebellothalamic tractotomy experienced reversible vestibular symptoms, but only during the final, highest-power sonications

MRgFUS neurosurgery requires the attachment of a metal stereotactic head frame to keep the patient's head absolutely still and to facilitate precise localization of the target area for ablation. In their 2013 study, Elias et al³⁷ reported a few minor adverse effects associated with use of the frame, including the pins used to secure the frame. Among the 15 participants, there were four (27%) headaches lasting more than 24 hours; four (27%) instances of scalp numbness; one pin-site laceration (7%); one instance of swelling around the eyes; and two scalp burns from pin-site MRI heating (13%).³⁷ All events resolved without intervention.³⁷

The study by Zaaroor et al⁴⁵ included participants with essential tremor and other movement disorders. The authors reported overall adverse effects for the study population but did not provide separate findings for the subset of participants with essential tremor ($n = 18$). The authors reported occurrences of postoperative gait ataxia ($n = 3$; resolved within 1–3 months) and hand ataxia ($n = 2$; resolved within 1–4 weeks). All cases were transient and resolved gradually.⁴⁵ The relative frequency of these events among participants with essential tremor is unclear.

Tables 15 and 16 summarize the adverse effects reported in the cohort studies, and in the intervention arm and unblinded cohort of the 2016 randomized controlled trial of ventral intermediate nucleus thalamotomy for the treatment of essential tremor by Elias et al.³⁸

Table 15: Adverse Effects Reported in Studies of MRgFUS Ventral Intermediate Nucleus Thalamotomy

Author, Year (n)	Time Point	Paresthesias or Numbness, n (%)	Gait or Motor Disturbance, n (%)	Speech Problems, n (%)	Headache, n (%)	Vestibular Issues, n (%)	Other, n (%)
Elias et al, 2016 ^{38,a} <i>Randomized to MRgFUS (n = 56)</i>	Total ^b	Face and hand, 6 (11) Face, lips, and tongue, 8 (14) Hand and fingers, 6 (11) Leg, 1 (2)	Ataxia, 11 (20) Subjective unsteadiness, 9 (16) Dysmetria, 7 (12)	Dysarthria, 1 (2) Dysphagia, 1 (2)	> 1 day, 8 (14)	Disequilibrium sensation, 5 (9) Tinnitus, 3 (5)	Contralateral weakness, 2 (4) Fatigue, 3 (5) Taste disturbance, 3 (5)
	12 mo	Face and hand, 8 (14) Face, lips, and tongue, 5 (9) Hand and fingers, 2 (4) Leg, 0	Ataxia, 2 (4) Subjective unsteadiness, 3 (5) Dysmetria, 2 (4)	Dysarthria, 0 Dysphagia, 0	–	Disequilibrium sensation, 1 (2) Tinnitus, 0	Contralateral weakness, 1 (2) Fatigue, 0 Taste disturbance, 2 (4)

Author, Year (n)	Time Point	Paresthesias or Numbness, n (%)	Gait or Motor Disturbance, n (%)	Speech Problems, n (%)	Headache, n (%)	Vestibular Issues, n (%)	Other, n (%)
Elias et al, 2016 ^{38,b} <i>Unblinded crossover cohort</i> (n = 21)	Total ^c	Face, lips, and tongue, 6 (29) Hand and fingers, 5 (24)	Ataxia, 3 (14) Subjective unsteadiness, 5 (24) Dysmetria, 3 (14)	Dysarthria, 3 (14)	Any, 7 (33)	Disequilibrium sensation, 3 (14)	Contralateral weakness, 3 (14) Fatigue, 4 (19) Taste disturbance, 2 (10)
	12 mo	Face, lips, and tongue, 5 (24) Hand and fingers, 1 (5)	Ataxia, 0 Subjective unsteadiness, 1 (5) Dysmetria, 2 (10)	Dysarthria, 2 (10)	Any, 0	Disequilibrium sensation, 1 (5)	Contralateral weakness, 1 (5) Fatigue, 0 Taste disturbance, 2 (10)
Chang et al, 2015 ³⁶ (n = 11)	1 mo	—	—	—	—	Mild balance problem, 1 (9)	—
Elias et al, 2013 ³⁷ (n = 15)	Post-operative	Lip or tongue, 9 (60) Finger, 5 (33)	Ataxia, 4 (27) Subjective unsteadiness, 5 (33) Dysmetria, 1 (7)	Slurred speech (dysarthria), 1 (7)	—	—	Weak grip, 1 (7)
	12 mo	Lip or tongue, 2 (13) Finger, 1 (7)	Ataxia, 0 Subjective unsteadiness, 0 Dysmetria 0	Slurred speech (dysarthria), 0	> 1 day, 0	—	Weak grip, 0

Author, Year (n)	Time Point	Paresthesias or Numbness, n (%)	Gait or Motor Disturbance, n (%)	Speech Problems, n (%)	Headache, n (%)	Vestibular Issues, n (%)	Other, n (%)
Lipsman et al, 2013 ⁴¹ (n = 4)	3 mo	Thumb and index finger, 1 (20)	—	—	—	—	—

Abbreviation: MRgFUS, magnetic resonance-guided focused ultrasound.

Note: The adverse effects described include all those as reported in the published articles.

^aThe events reported are those occurring in the MRgFUS arm of the randomized controlled trial. Events at 12 months persist.

^bThe events reported are those occurring in the unblinded cohort of crossover participants from the sham arm. Events at 12 months persist.

^cThe total reflects the sum of all events occurring any time during the 3-month randomized study period.

Among the studies of MRgFUS ventral intermediate nucleus thalamotomy, the most common adverse effects were paresthesias or numbness in the face or fingers and, more rarely, gait or motor disturbances. About half of participants in these studies experienced one or more adverse effects immediately following the MRgFUS procedure. Most adverse effects occurred shortly after the procedure were transient, related to postoperative edema (swelling near the lesion site following surgery), resolving by follow-up in most cases. Across the studies' 107 participants, persistent adverse effects included paresthesias in 1% to 14%, gait or motor disturbance in up to 7%, balance problems or disequilibrium in less than 1%, contralateral weakness in less than 1%, and taste disturbance in up to 2%.^{36-38,41}

Two studies reported data on the adverse effects of MRgFUS cerebellothalamic tractotomy, the most frequent of which was gait instability (either new or an exacerbation of pre-existing instability).^{39,42} With the exception of one participant in the study by Gallay et al,³⁹ who had persistent mild gait instability (i.e., a worsening of 0.5 points out of a possible 4 from baseline), all adverse effects completely resolved by follow-up, as shown in Table 16.

Table 16: Adverse Effects Reported in Studies of MRgFUS Cerebellothalamic Tractotomy

Author, Year (n)	Time Point	Paresthesias or numbness, n (%)	Gait or Motor Disturbance, n (%)	Speech Problems, n (%)	Headache, n (%)	Vestibular Issues, n (%)	Other, n (%)
Schreglmann et al, 2017 ⁴² (n = 6)	Postoperative ^a	—	Gait instability, 1 (17) Clumsiness of treated hand, 1 (17)	—	—	Tendency to veer to treated side, 1 (17)	—
	3 mo	—	Gait instability, 0 Clumsiness of treated hand, 0	—	—	Tendency to veer to treated side, 0	—
Gallay et al, 2016 ³⁹ (n = 21)	Postoperative ^a	—	Worsening of pre-existing gait instability, 5 (24)	—	—	—	—
	Last follow-up ^{a,b}	—	Worsening of pre-existing gait instability, 1 (5); 0.5/4 points worse than baseline)	—	—	—	—

Abbreviation: MRgFUS, magnetic resonance-guided focused ultrasound.

Note: The adverse effects described include all those as reported in the published articles.

^aThe exact time point was not reported.^bThe last follow-up ranged from 3 months to 1 year after surgery.

MRgFUS Thalamotomy Versus Sham

In the 2016 randomized controlled trial by Elias et al,³⁸ six participants who underwent MRgFUS thalamotomy (11%) and 8 who underwent a sham procedure (40%) experienced no adverse effects. Table 17 summarizes the occurrence of adverse effects over the 3-month randomized study period for each group.

Table 17: Adverse Effects Reported Over 3 Months in a Randomized Controlled Trial of MRgFUS Thalamotomy Versus Sham

Adverse Effect	MRgFUS (N = 56), Total ^a n (%)	Sham (N = 20), Total ^a n (%)
Procedural Events		
Head discomfort	17 (30)	0
Stereotactic frame pin-site edema, pain, or bruising	17 (30)	7 (35)
Vertigo	12 (21)	0
Nausea	11 (20)	2 (10)
Back pain	5 (9)	1 (5)
Scalp tingling	4 (7)	1 (5)
Anxiety	3 (5)	2 (10)
Vomiting	2 (4)	0
Paresthesias or Numbness		
Face, lips, and tongue	8 (14)	0
Face and hand	6 (11)	0
Hand and fingers	6 (11)	1 (5)
Leg	1 (2)	0
Gait or Motor Disturbance		
Ataxia	11 (20)	0
Subjective unsteadiness	9 (16)	1 (5)
Dysmetria	7 (12)	0
Speech Problems		
Dysarthria	1 (2)	0
Dysphagia	1 (2)	0
Vestibular Symptoms		
Disequilibrium sensation	5 (9)	0
Tinnitus	3 (5)	0
Other Effects		
Headache lasting more than 1 day	8 (14)	4 (20)
Fatigue	3 (5)	1 (5)
Taste disturbance	3 (5)	0
Contralateral weakness	2 (4)	0

Abbreviations: MRgFUS, magnetic resonance-guided focused ultrasound; N, number of participants in the group; n, number of events reported.

^aThe total reflects the sum of all events occurring any time during the 3-month randomized study period.

Source: Elias et al, 2016.³⁸

MRgFUS Thalamotomy Versus Deep Brain Stimulation

Huss et al⁴⁰ retrospectively compared MRgFUS thalamotomy with bilateral and unilateral deep brain stimulation. Table 18 presents the transient adverse effects (occurring within 0–3 months of the procedure) and long-term adverse effects (occurring at 12 months following the procedure) reported for each of the three procedures.

Table 18: Adverse Effects Reported in a Study Comparing MRgFUS Thalamotomy With Unilateral and Bilateral Deep Brain Stimulation

Adverse Effect	MRgFUS (N = 15), n transient (n at 12 mo)	Bilateral DBS (N = 57), n transient (n at 12 mo)	Unilateral DBS (N = 13), n transient (n at 12 mo)
Procedural Events			
Vertigo	11 (0)	0 (0)	0 (0)
Headache	9 (0)	0 (0)	0 (0)
Nausea or vomiting	8 (0)	0 (0)	0 (0)
Warm or flushed feeling	4 (0)	0 (0)	0 (0)
Stereotactic frame pin-site burn	2 (0)	0 (0)	0 (0)
Side Effects			
Paresthesia (any)	14 (3)	2 (1)	1 (2)
Gait instability	5 (0)	10 (0)	11 (0)
Dysarthria	1 (0)	10 (6)	1 (0)
Weakness	1 (0)	4 (1)	1 (0)
Dysphagia	0 (0)	2 (0)	0 (0)
Mental status change	0 (0)	3 (3)	1 (0)
Complications			
DBS hardware infection	NA	0 (1)	0 (0)
DBS lead erosion	NA	1 (2)	0 (0)
Hemorrhage	0 (0)	2 (0)	0 (0)

Abbreviations: DBS, deep brain stimulation; MRgFUS, magnetic resonance-guided focused ultrasound; N, number of participants in the group; n, number of events reported.

Source: Adapted from Huss et al, 2015.⁴⁰

Huss et al⁴⁰ did not statistically quantify the frequency of the side effects and complications associated with MRgFUS neurosurgery or deep brain stimulation. As depicted in Table 18, the most common transient adverse effects of MRgFUS thalamotomy were paresthesias and gait instability; however, at 1 year post-procedure, the majority (nearly 85%) of these occurrences had resolved.⁴⁰ There were no serious complications associated with MRgFUS thalamotomy in the study. The most common adverse effects associated with deep brain stimulation were gait instability and dysarthria, of which about half of the latter persisted at 12 months post-surgery.⁴⁰ Mental state changes were not seen in any patients who had undergone MRgFUS, but did occur among patients who had undergone deep brain stimulation. All instances of mental status change persisted in the bilateral deep brain stimulation group at 12 months.⁴⁰ In the bilateral deep brain stimulation group, hardware complications occurred in four instances over 12 months, and two intracranial hemorrhages occurred. Among patients who had undergone unilateral deep brain stimulation, two paresthesias developed over 12 months.⁴⁰

The authors reported that the incidence and resolution of the adverse effects associated with MRgFUS thalamotomy and deep brain stimulation that occurred in the study were consistent with previously reported adverse event profiles for these procedures.⁴⁰ However, they did not conduct a statistical analysis.

MRgFUS Thalamotomy Versus Deep Brain Stimulation or Radiofrequency Thalamotomy

In a retrospective study, Kim et al⁴⁶ analyzed the rates of adverse effects associated with unilateral MRgFUS thalamotomy, deep brain stimulation, and radiofrequency thalamotomy by reviewing the charts of patients with essential tremor who had undergone these surgeries. For deep brain stimulation, the authors considered complications to include both side effects that were modifiable by adjusting the stimulation settings and those that were non-modifiable. Of the 59 patients in the study, 31 (52.5%) did not experience any postoperative or persistent adverse effects.⁴⁶

Ten participants in the radiofrequency thalamotomy group (58.5%), one in the deep brain stimulation group (5.3%), and one in the MRgFUS thalamotomy group (4.3%) experienced adverse effects within 1 month following surgery. At 12 months, the numbers of participants experiencing persistent adverse effects were as follows: two (11.7%) who had undergone radiofrequency thalamotomy, four (21.1%) who had undergone deep brain stimulation (including both modifiable and non-modifiable complications), and one (4.3%) who had undergone MRgFUS thalamotomy.⁴⁶

The authors compared occurrence rates of adverse effects between the three groups at 1 and 12 months post-procedure. A generalized estimating equation model found a statistically significant difference in complication rates between the groups at each time point ($P = .01$).⁴⁶ The authors counted more than two adverse effects in a given patient as one. Table 19 lists the frequency of adverse effects associated with each surgery.

Table 19: Adverse Effects Reported in a Study Comparing MRgFUS Thalamotomy, Deep Brain Stimulation, and Radiofrequency Thalamotomy

Follow-Up	MRgFUS (N = 23), n ^a (%)	Deep Brain Stimulation (N = 19), n ^a (%)	Radiofrequency Thalamotomy (N = 17), n ^a (%)
1 month	Mild facial paresis, 1 (4.3) Balance problems, 1 (4.3) Loss of taste, 1 (4.3)	Mild facial paresis, 1 (5.3)	Mild facial paresis, 3 (17.6) Intracerebral hemorrhage, 2 (11.8) Loss of taste, 1 (5.9) Cognitive deterioration, 1 (5.9) Mild dysarthria, 5 (29.4) Hypesthesia, 1 (5.9)
12 months	Very mild facial paresis, 1 (4.3)	Balance problems, ^b 3 (15.8) Forearm muscle twitch, 1 (5.3)	Mild facial paresis, 1 (5.9) Mild dysarthria, 1 (5.9)

Abbreviations: MRgFUS, magnetic resonance-guided focused ultrasound; N, number of patients in the group; n, number of events reported.

^aRepresents the number of events experienced; more than one adverse effect may have been experienced by an individual patient. More than two complications in a single patient were counted as one.

^bConsidered to be a modifiable side effect, which was resolved by adjusting the stimulation settings.

Source: Adapted from Kim et al 2017.⁴⁶

At the 1 month follow-up, the complication rates were 13% (n = 3) in the MRgFUS thalamotomy group, 5.3% (n = 1) in the deep brain stimulation group, and 58.8% (n = 10) in the radiofrequency thalamotomy group. At 12 months, the complication rates were 4.4% (n = 1) for MRgFUS thalamotomy, 21.1% (n = 4) for deep brain stimulation, and 11.8% (n = 2) for radiofrequency thalamotomy.⁴⁶ Post-hoc analyses determined that the complication rate was significantly lower in the deep brain stimulation group than in the radiofrequency thalamotomy group ($P < .001$). At 12 months, the lowest complication rate of all three surgeries occurred in the MRgFUS thalamotomy group; this rate was statistically significantly lower than for both deep brain stimulation ($P < .01$) and radiofrequency thalamotomy ($P < .01$).⁴⁶ When only the non-modifiable complications associated with deep brain stimulation were included in the analysis, there was no longer a statistically significant difference between the complication rates for MRgFUS thalamotomy and deep brain stimulation.⁴⁶

Table 20 provides the GRADE assessment of the complication rate analysis from the study by Kim et al.⁴⁶

Table 20: GRADE Evidence Profile for the Comparison of MRgFUS Thalamotomy, Deep Brain Stimulation, and Radiofrequency Thalamotomy

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Treatment-Related Complication Rate							
1 (Observational) ⁴⁶	Serious limitations (–1) ^a	No serious limitations ^b	No serious limitations	No serious limitations	Undetected ^b	NA	⊕ Very Low

Abbreviations: MRgFUS, magnetic resonance-guided focused ultrasound; NA, not applicable.

^aRisk of bias was highest owing to retrospective data collection methods. The full risk-of-bias assessment is presented in Appendix 2, Table A2.

^bCannot definitively assess presence or absence because the evidence is derived from a single study.

Serious Adverse Events

A small number of serious adverse events were reported in the included studies. In the 2013 pilot study by Elias et al,³⁷ one participant experienced dysesthesia of the index finger (abnormal sensation that can manifest as pain or discomfort), which began within 3 months of undergoing MRgFUS ventral intermediate nucleus thalamotomy and persisted to 12 months. In the study by Lipsman et al,⁴¹ one participant developed lower-leg deep vein thrombosis 1 week after undergoing MRgFUS ventral intermediate nucleus thalamotomy, which may have been related to the long duration of the procedure (i.e., 5–6 hours). In response, this person was treated with anticoagulant therapy for 3 months. In the study of MRgFUS cerebellothalamic tractotomy by Schreglmann et al,⁴² one participant experienced a fall at home 4 weeks after the procedure that required hospitalization; they then made a full recovery. However, the authors later discovered that this participant had also experienced an unexplained fall 6 months prior to surgery. The article reporting on the 2016 randomized controlled trial by Elias et al³⁸ provides a full list of adverse events determined to be unrelated to the study interventions.

Discussion

MRgFUS neurosurgery significantly reduces tremor and functional disability, improves quality of life, and has a favorable safety profile for people with medication-refractory, disabling essential tremor. We identified some evidence that people with predominant unilateral upper extremity tremor may experience the most benefit from MRgFUS neurosurgery. However, the evidence showed that those with some bilateral or axial tremor also experienced clinically meaningful improvements in tremor severity, quality of life, and functional independence following MRgFUS neurosurgery. The included studies were conducted in many international settings, including Ontario, so the findings can be generalized to local practice.

In Ontario, people with moderate to severe, medication-refractory essential tremor may pursue one of three neurosurgical options as the next line treatment following medication: radiofrequency thalamotomy, deep brain stimulation, or Gamma Knife thalamotomy. Although Gamma Knife thalamotomy is a noninvasive procedure, it is recommended only for very select patients, owing to its considerable unpredictability, risk of complications, and modest therapeutic effect. Therefore, people with medication-refractory, moderate to severe essential tremor who are unable to undergo an invasive surgery owing to contraindications or who find the risks involved unacceptable currently have no effective treatment options. MRgFUS neurosurgery, a noninvasive procedure, would provide an option for these people. In particular, the elderly, who are disproportionately affected by moderate to severe essential tremor, as well as people with multiple comorbidities, currently experience inequitable access to effective treatment that could be mitigated with access to MRgFUS neurosurgery.

Further, people with essential tremor who have no contraindications to invasive neurosurgery may choose not to undergo such a procedure for many reasons, including finding craniotomy, general anaesthetic, or implanted hardware unacceptable. With radiofrequency thalamotomy infrequently being performed anymore, deep brain stimulation has become the favoured option and the standard of care in many jurisdictions, as it is an effective and titratable treatment for essential tremor. However, people may be unable to comply with the intensive follow-up regime of adjustments to the stimulation settings, which can render this option unfeasible for some, particularly in terms of geography, mobility, and social support. We did not assess each surgical option separately because the question of which is the optimal neurosurgery for essential tremor was beyond the scope of this review.

Our findings are consistent with previous research findings that MRgFUS neurosurgery improves tremor, function, and quality of life and has a generally satisfactory safety profile.^{10,48,49} While the ideal outcome of MRgFUS neurosurgery would be to achieve total remission in tremor, there is no precise magnitude of improvement that is broadly considered a success. However, a tremor reduction of around 50% often enables people to perform key tasks that they were unable to perform before, such as drinking or writing, even if with some difficulty. With this degree of improvement, people can typically return to living more independently, engaging in social activities, and possibly working. The most common persistent adverse effect of MRgFUS neurosurgery, paresthesia, tends to resolve sufficiently that it does not interfere with people's daily lives. The loss of some treatment effect over time in some people can be expected because essential tremor is a progressive condition, and tremor is likely to recur with any therapy.¹²

There are some limitations to our review. First, although each study we reviewed found a clinically meaningful magnitude of effect in patient-important outcomes following MRgFUS neurosurgery, the sample sizes of these studies were small. Unfortunately, owing to methodological heterogeneity between studies, we could not meta-analyze these data. A challenge in assessing this body of literature is the variability in the reporting of outcome data and analyses. In the studies we reviewed, the measures of variance were inconsistently reported, the use of statistical comparisons varied, and it was unclear in many instances whether the study design fell under a cohort study or case series. We therefore took an inclusive approach to be comprehensive in our review.

Second, a pervasive issue in this field of research is the issue of unblinded outcome assessment. This potential methodological problem has particularly been quantified in studies of Gamma Knife thalamotomy whereby open-label trials have tended to find marked improvement, whereas blinded trials have found little or modest effect.⁵⁰ However, estimates tend to be more consistent between blinded and unblinded evaluations of outcomes of radiofrequency thalamotomy.⁵¹ While it is unclear to what extent this issue affected our review, three studies explicitly blinded outcome assessors, and results were consistent irrespective of blinding across the studies.

Third, comparative data against other surgeries were scant, and we identified only one randomized controlled trial demonstrating efficacy compared with sham. This is a widespread limitation in this field; no studies have been published comparing deep brain stimulation with sham procedures since its introduction decades ago.¹²

Fourth, the duration of follow-up among the studies was relatively short, varying from 1 to 12 months. Such limited follow-up precludes characterization of the long-term durability or adverse effects of the procedure. Future studies with longer follow-up are needed to provide insight into the longevity of therapeutic and adverse effects. This is an active area of research, and MRgFUS neurosurgery continues to be studied in essential tremor and other tremor conditions,⁵² as well as in other patient populations, such as people with chronic neuropathic pain.⁵³

Ongoing Studies

Two forthcoming studies registered on ClinicalTrials.gov may be relevant to this topic. One is an open-label, continued-access protocol to assess primarily intraoperative adverse events and also effectiveness via the CRST up to 12 months after MRgFUS thalamotomy in people with essential tremor (NCT02289560; last updated March 28, 2017; study completion December 2017). The second is an international registry to assess the effectiveness of MRgFUS neurosurgery in people with a movement disorder or neuropathic pain at 5 years following treatment (NCT03100474; last updated April 3, 2017; study completion 2024).

Conclusions

MRgFUS neurosurgery is an effective treatment for moderate to severe, medication-refractory essential tremor and has an acceptable safety profile. Specifically:

- In noncomparative studies, MRgFUS neurosurgery has been found to significantly improve tremor severity and quality of life and to significantly reduce functional disability in daily activities (low certainty in the evidence); MRgFUS neurosurgery has been found to be significantly more effective than a sham procedure (high certainty in the evidence)
- There are no significant differences in tremor severity or quality-of-life improvement or in functional disability reduction conferred by MRgFUS neurosurgery compared with deep brain stimulation (very low certainty in the evidence)
- There is no significant difference in tremor severity improvement conferred by MRgFUS neurosurgery compared with radiofrequency thalamotomy (very low certainty in the evidence)
- MRgFUS neurosurgery is associated with few complications and adverse effects according to noncomparative studies and when compared with radiofrequency thalamotomy and deep brain stimulation (very low certainty in this evidence); the vast majority of adverse effects are transient and resolve either entirely or to a point at which there is minimal interference with people's lives

ECONOMIC EVIDENCE

Research Question

What is the cost-effectiveness of magnetic resonance-guided focused ultrasound (MRgFUS) neurosurgery compared with standard care for the treatment of moderate to severe, medication-refractory essential tremor?

Methods

Economic Literature Search

We performed an economic literature search on April 11, 2017, for studies published from inception to the search date. To retrieve relevant studies, we developed a search using the clinical search strategy with an economic and costing filter applied.

We created database auto-alerts in MEDLINE and Embase and monitored them for the duration of the health technology assessment.

We performed a targeted grey literature search of health technology assessment agency websites, clinical trial registries, and the Tufts Cost-Effectiveness Analysis Registry. See Clinical Evidence, Literature Search, above, for further details on the methods used. See Appendix 1 for the literature search strategies, including all search terms.

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using the DistillerSR management software and then obtained the full text of studies that appeared eligible for the review, according to the inclusion criteria. The author then examined the full-text articles and selected studies eligible for inclusion. We also examined reference lists for any additional relevant studies not identified through the search.

Inclusion Criteria

- English-language full-text publications
- Studies in people with moderate to severe, medication-refractory essential tremor
- Studies reporting on MRgFUS neurosurgery compared with no surgery or with other surgical procedures for essential tremor
- Cost–utility, cost-effectiveness, cost–benefit, cost–consequence, or cost analyses

Exclusion Criteria

- Narrative reviews, letters/editorials, case reports, commentaries, abstracts, posters, or unpublished studies

Outcomes of Interest

- Incremental cost-effectiveness ratio
- Incremental costs
- Incremental effectiveness

Data Extraction

We extracted relevant data on the following:

- Source (i.e., name, location, year)
- Population and comparator
- Interventions
- Outcomes (i.e., health outcomes, costs, incremental cost-effectiveness ratio)

We contacted study authors to provide clarification as needed (Ravikumar et al,⁵⁴ Martinez-Martin et al⁵⁵).

Study Applicability and Methodological Quality

We identified one study⁵⁴ and determined its usefulness for decision-making by applying a modified quality appraisal checklist for economic evaluations originally developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom. The original checklist is used to inform the development of clinical guidelines by NICE.⁵⁶ We modified the wording of the questions to remove references to guidelines and to make it Ontario specific. We also separated the checklist into two sections. The first section assesses the applicability of studies to the research question as directly applicable, partially applicable, or not applicable. For studies deemed directly applicable or partially applicable to the research question, we assess their methodological quality using the second section of the checklist. Based on this assessment, we consider each study to have minor limitations, potentially serious limitations, or very serious limitations (Appendix 4, Tables A4 and A5).

Results

Literature Search

The literature search yielded 31 citations published from inception to April 11, 2017, after removing duplicates. We excluded 30 articles based on information in the title and abstract. We then obtained the full text of the one potentially relevant article for further assessment, and this study met the inclusion criteria.⁵⁴ We also hand-searched the reference list of the included study but did not find any additional eligible studies. Figure 4 presents the flow diagram for the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).

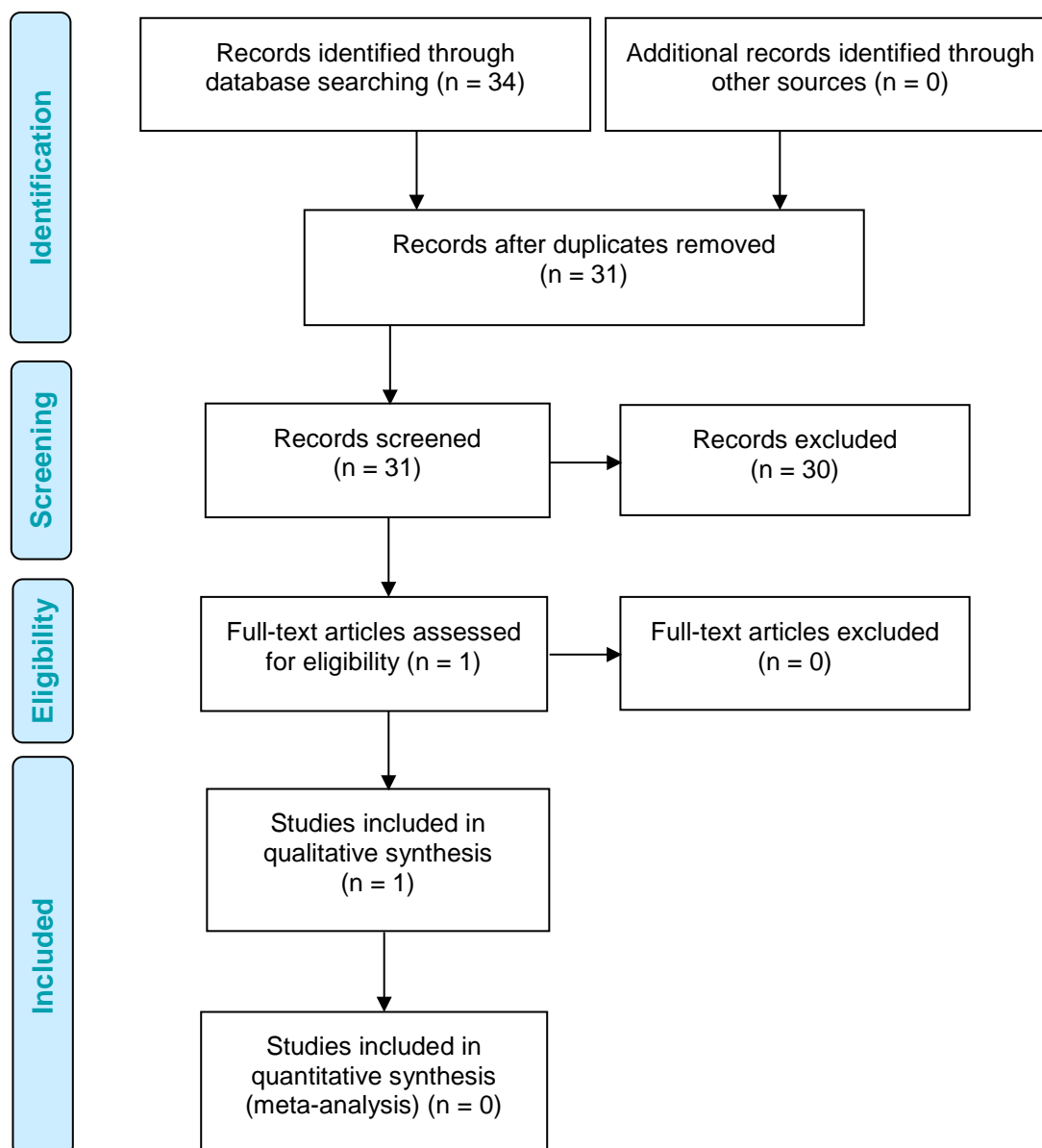


Figure 4: PRISMA Flow Diagram—Economic Search Strategy

Source: Adapted from Moher et al.³¹

Review of the Included Economic Study

Table 21 provides a summary of the included study. In this study, Ravikumar et al⁵⁴ conducted a cost-effectiveness analysis and systematic review of 32 studies that examined treatment effectiveness and treatment-related complications. The outcomes of interest were total costs, total quality-adjusted life years (QALYs), and incremental cost per QALY. The authors used a decision tree model to perform a cost-utility analysis of MRgFUS thalamotomy compared with deep brain stimulation and stereotactic radiosurgery (e.g., Gamma Knife) in the United States. Deep brain stimulation was modeled as unstaged (consisting of one operation) or staged (consisting of two operations). The model population was people with medication-refractory essential tremor. The authors defined treatment effectiveness as percent improvement in

functional disability, assessed via part C of the Fahn–Tolosa–Marín (FTM) Clinical Rating Scale for Tremor or the Clinical Rating Scale for Tremors (CRST). The model used a U.S. societal perspective. Time horizon was not reported but appears to be less than 1 year based on the results reported.

The results showed that MRgFUS thalamotomy was more effective and less expensive than both unstaged and staged deep brain stimulation.⁵⁴ Compared with stereotactic radiosurgery, the least costly procedure, MRgFUS thalamotomy was associated with an incremental cost of \$580 and an incremental QALY of 0.078, resulting in an incremental cost-effectiveness ratio (ICER) of \$7,436 per QALY gained.⁵⁴ The ICER of unstaged deep brain stimulation versus stereotactic radiosurgery was estimated to be \$483,500 per QALY gained, because deep brain stimulation is more expensive (by \$7,893) and only slightly more effective (an additional 0.018 QALYs gained).⁵⁴ Two-way sensitivity analyses showed that the ICER of MRgFUS thalamotomy versus stereotactic radiosurgery was sensitive to assumptions regarding the relative cost and effectiveness of MRgFUS thalamotomy compared with stereotactic radiosurgery.⁵⁴

Table 21: Results of Economic Literature Review—Summary

Author, Year, Location	Study Design and Perspective	Population	Interventions	Results		
				Health Outcome, QALYs (SD)	Costs, 2017 USD (SD)	Cost-Effectiveness
Ravikumar et al, 2017, United States ⁵⁴	<ul style="list-style-type: none"> • Cost–utility analysis • Decision tree model • Time horizon: not reported but assumed to be less than 1 year based on the results • U.S. societal perspective 	<ul style="list-style-type: none"> • People with medication-refractory essential tremor 	<ul style="list-style-type: none"> • MRgFUS thalamotomy • Deep brain stimulation, unstaged • Deep brain stimulation, staged • Stereotactic radiosurgery 	<ul style="list-style-type: none"> • MRgFUS: 0.194 (0.005) • DBS, unstaged: 0.134 (0.003) • DBS, staged: 0.134 (0.003) • SRS: 0.116 (0.003) 	<ul style="list-style-type: none"> • MRgFUS: \$20,593 (\$1,402) • DBS, unstaged: \$27,906 (\$524) • DBS, staged: \$45,107 (\$614) • SRS: \$20,013 (\$1,036) 	<ul style="list-style-type: none"> • MRgFUS dominates DBS (more effective, less costly) • ICER, unstaged DBS vs. SRS: \$483,500/QALY • ICER, staged DBS vs. SRS: \$1,476,118/QALY (calculated based on results reported) • ICER, MRgFUS vs. SRS: \$7,436/QALY (calculated based on results reported)

Abbreviations: DBS, deep brain stimulation; ICER, incremental cost-effectiveness ratio; MRgFUS, magnetic resonance-guided focused ultrasound; QALY, quality-adjusted life-year; SD, standard deviation (from probabilistic analysis); SRS, stereotactic radiosurgery.

Applicability and Methodological Quality of the Included Study

Appendix 4 provides the results of the methodology checklist for economic evaluations applied to the included study.⁵⁴ We considered this study only partially applicable to our research question because it was conducted from a U.S. perspective and did not include all treatments available in Ontario (i.e., it did not assess radiofrequency thalamotomy). Although the authors used valid methods to conduct their cost–utility analysis, we considered the study to have minor limitations. In particular, it did not include long-term clinical outcomes such as tremor recurrence. Further, the authors did not specify the time horizon of the model, and they did not clearly report the methods used to derive comparative treatment effectiveness and utility values.

Discussion

Ravikumar et al⁵⁴ estimated the effectiveness of MRgFUS thalamotomy, deep brain stimulation (unstaged and staged), and stereotactic radiosurgery for the treatment of medication-refractory essential tremor based on a systematic review and meta-analysis of relevant clinical studies. However, the authors did not explicitly report the results of their meta-analysis. Aside from one phase III randomized controlled trial of MRgFUS thalamotomy,³⁸ all studies reviewed by the authors included evidence based on uncontrolled observational studies, which may have introduced biases into the cost-effectiveness results.

Another limitation of this study is that the authors did not clearly state the method used to derive utilities. The authors suggested that utilities of essential tremor could be derived from percent change in functional disability using a mapping algorithm. However, they did not report or reference data supporting the mapping algorithm, nor did they report the baseline (pre-surgery) utility value.

In addition, since the study was conducted from a U.S. perspective and costs were based on U.S. Medicare reimbursement rates, we deemed its findings not generalizable to the Ontario setting.

Conclusions

We identified one economic study suggesting that MRgFUS thalamotomy may be cost-effective compared with deep brain stimulation and stereotactic radiosurgery for the treatment of medication-refractory essential tremor. However, this study has some methodological limitations and is not applicable to the Ontario setting.

PRIMARY ECONOMIC EVALUATION

Although the published economic evaluation that we identified in the literature review addressed the interventions of interest, it did not take a Canadian or Ontario-specific perspective. Owing to this and the methodological limitations described, we conducted a primary economic evaluation using Ontario-specific costs and clinical care pathways.

Through consultation with clinical experts, we determined a priori that there are two subgroups within our target population of people with moderate to severe, medication-refractory essential tremor: (1) those who are ineligible for invasive neurosurgeries owing to contraindications or preference; and (2) those who are eligible for invasive neurosurgeries (see the Clinical Evidence section for more details on this subgroup). Therefore, we formulated the following two research questions.

Research Questions

1. What is the cost-effectiveness of MRgFUS neurosurgery compared with standard treatment (i.e., no surgery) for people with moderate to severe, medication-refractory essential tremor, who are ineligible for invasive neurosurgery, within the context of the Ontario Ministry of Health and Long-Term Care?
2. What is the cost-effectiveness of MRgFUS neurosurgery compared with standard treatment (i.e., radiofrequency thalamotomy or deep brain stimulation) for people with moderate to severe, medication-refractory essential tremor, who are eligible for invasive neurosurgery, within the context of the Ontario Ministry of Health and Long-Term Care?

Methods

The information presented in this report follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards Statement.⁵⁷

Type of Analysis

We conducted a cost–utility analysis to determine the costs and health outcomes (i.e., QALYs) associated with each treatment strategy. We chose this type of analysis because utility inputs are available and a generic outcome measure such as QALYs allows decision-makers to make comparisons across different conditions and interventions. The outcomes reported are total costs and total QALYs for each treatment and incremental cost per QALY gained compared with the next most effective strategy.

Target Population

The population evaluated in the model was people with moderate to severe, medication-refractory, disabling essential tremor; we then divided this population into two subgroups: those ineligible for invasive neurosurgery and those eligible for invasive neurosurgery. We based patient characteristics on the 2016 phase III randomized controlled trial of MRgFUS thalamotomy by Elias et al.³⁸ We validated these characteristics via clinical experts (in-person communication, May 25, 2017; telephone communication, May 30 and 31, 2017) as representative of the Canadian population. At the start of the model, the average age of the population was 71 years, and the majority were male (68%).

Perspective

For the reference case, we conducted the analyses from the perspective of the Ontario Ministry of Health and Long-Term Care.

Since treatment for essential tremor may improve people's motor control, possibly allowing them to return to work, we also conducted scenario analyses incorporating people's out-of-pocket and lost productivity costs from a societal perspective.

Intervention and Comparators

Thalamotomy and deep brain stimulation are both effective treatments for moderate to severe, medication-refractory essential tremor.^{10,58} Thalamotomy works by creating a permanent injury to the part of the brain causing the tremor, whereas deep brain stimulation involves using an implanted electrode or electrodes to block the brain activity causing the tremor. Thalamotomy can be performed invasively (e.g., via radiofrequency) or noninvasively (e.g., via MRgFUS or Gamma Knife). Thalamotomy is typically performed unilaterally, whereas deep brain stimulation can be performed unilaterally or bilaterally. The treatments have different adverse effect profiles.¹⁷ Radiofrequency thalamotomy and deep brain stimulation involve craniotomy and therefore involve the risks of open surgical procedures, such as infection and intracranial hemorrhage. MRgFUS and Gamma Knife thalamotomy are noninvasive but involve making a permanent lesion in the brain.⁵⁹ Deep brain stimulation is the current surgical standard of care because it is considered reversible and adjustable. However, the implanted device requires long-term management, including repeat programming and periodic battery replacement. Deep brain stimulation is also associated with hardware-related complications such as lead fracture and migration and device malfunction.^{17,60} Owing to these limitations, there is an unmet need for less invasive surgical options for the treatment of essential tremor.⁶¹

For research question 1, we compared MRgFUS thalamotomy with no surgery based on the 2016 phase III randomized controlled trial comparing MRgFUS thalamotomy with a sham procedure by Elias et al.³⁸ For people ineligible for invasive neurosurgery, Gamma Knife thalamotomy is a surgical option. However, there is insufficient evidence regarding the effectiveness and safety of this procedure.¹⁶ Further, the clinical experts we consulted do not view Gamma Knife as an effective treatment option owing to its uncertain effectiveness and high risk of adverse effects. Therefore, we excluded Gamma Knife as a comparator.

For research question 2, we compared MRgFUS neurosurgery with radiofrequency thalamotomy and deep brain stimulation in people eligible for invasive neurosurgery.

On July 11, 2017, we performed a targeted literature search in MEDLINE and the Cochrane Database of Systematic Reviews for systematic reviews on the effectiveness and safety of radiofrequency thalamotomy and deep brain stimulation published from inception to the search date. See Appendix 1 for the literature search strategies, including all search terms. Based on the clinical literature^{16,20,40} and expert judgment (in-person communication, May 25 and June 19, 2017; telephone communication, May 30 and 31, 2017), we assumed that MRgFUS neurosurgery, radiofrequency thalamotomy, and deep brain stimulation are equally effective for tremor relief but have different adverse event profiles.

Table 22 summarizes the two reference case analyses.

Table 22: Reference Case Analysis Summary

Analysis	Patient Population	Intervention	Comparator(s)	Clinical Effectiveness Determination
Research question 1	People ineligible for invasive neurosurgery	MRgFUS neurosurgery	No surgery	Based on direct comparison only (1 RCT) ³⁸
Research question 2	People eligible for invasive neurosurgery	MRgFUS neurosurgery	Radiofrequency thalamotomy Deep brain stimulation	Based on indirect comparison ^{20,40} and clinical expert opinion: assumes all surgeries are equally effective for tremor improvement but have different adverse event profiles

Abbreviations: MRgFUS, magnetic resonance-guided focused ultrasound; RCT, randomized controlled trial.

Time Horizon and Discounting

In the reference case analyses, we used a 5-year time horizon to capture the long-term outcomes of the disease (e.g., tremor recurrence, reoperation, long-term complications). Although essential tremor is a chronic illness, we did not use a lifetime horizon because MRgFUS is a new technology and long-term clinical data are not yet available. We also explored different time horizons in scenario analyses (e.g., 1 year, 10 years).

We discounted both costs and outcomes at a rate of 1.5% per year, as per the Canadian Agency for Drugs and Technologies in Health guidelines for economic evaluations.⁶² Rates of 0% and 3% were considered in sensitivity analyses.

Model Structure

We developed a Markov model to estimate the long-term clinical and economic outcomes of MRgFUS neurosurgery versus standard treatment for people with moderate to severe, medication-refractory essential tremor. We used a cycle length of 1 year, as patients are usually monitored annually for disease progression. We applied a half-cycle correction on all health state transitions. Figure 5 illustrates the model structure. For research question 1, we compared MRgFUS neurosurgery with no surgery. For research question 2, we compared MRgFUS neurosurgery with radiofrequency thalamotomy and with deep brain stimulation; patients in the comparator arms followed the same clinical pathway and model structure as those in the MRgFUS arm.

The clinical pathway and Markov health states are as follows:

- All patients enter the model with disabling tremor
 - Patients in the “no-surgery” arm continue to live with disabling tremor and may die from natural causes in each model cycle
 - Patients in the “surgery” arm (i.e., those undergoing MRgFUS neurosurgery, radiofrequency thalamotomy, or deep brain stimulation) undergo surgery right away and enter the “improved tremor, post–primary surgery” health state
- Patients in the “improved tremor, post–primary surgery” health state may have one of two surgical outcomes: Some may experience marked tremor improvement (from 50% to 100% improvement compared with baseline), whereas others may experience mild to moderate improvement (from 10% up to 50% improvement). This categorization is based on the work of Fahn et al⁶

- In the first year post-surgery, some patients in the “improved tremor, post–primary surgery” health state may experience short-term adverse effects (i.e., side effects) or complications (e.g., temporary paresthesia that resolves within a few months). In addition, a certain proportion of patients in the “improved tremor, post–primary surgery” health state may experience long-term, permanent adverse effects (persisting for more than 1 year after surgery)
- Patients in the “improved tremor, post–primary surgery” health state may progress and enter one of two tremor recurrence states:
 - “Tremor recurrence, no reoperation”: Patients in this health state again experience disabling tremor but do not undergo a further surgery. According to clinical experts, the majority of patients do not undergo reoperation when tremor recurs (in-person communication, May 25, 2017; telephone communication, May 30 and 31, 2017)
 - “Tremor recurrence, reoperation”: Patients in this health state experience tremor recurrence and undergo a second surgery (the same type as the previous one) right away. Based on clinical expert opinion, patients who undergo a second surgery are usually treated with the procedure they received the first time. Patient quality of life differs based on the surgical outcome: marked improvement or mild to moderate improvement
- All patients in the “tremor recurrence, reoperation” health state enter the “improved tremor, post-reoperation” health state after 1 year if they do not die
- At any point during the model time frame, a patient may die from natural causes. Since essential tremor does not affect life expectancy,^{38,63} we used age-specific natural mortality

We developed the model using Microsoft Excel 2013 (Microsoft Corporation, Redmond, MA) and then replicated the analysis using TreeAge Pro 2017 (TreeAge Software, Williamstown, MA) for validation.

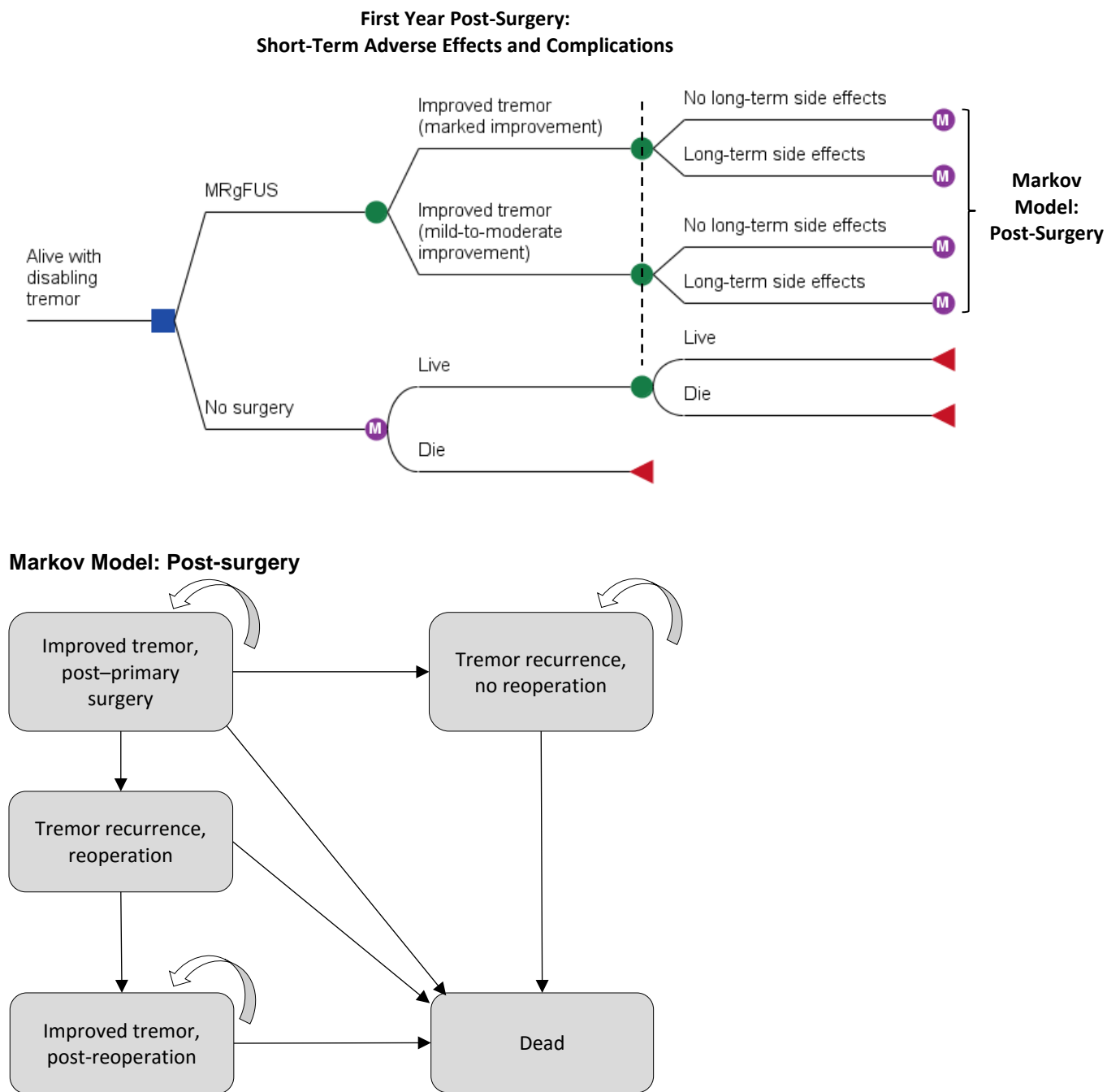


Figure 5: Cost–Utility Model

Main Assumptions

To simplify our analysis, we made the following assumptions:

- Since essential tremor is a slowly progressive disease, patients in the “no surgery” arm have stable disease and do not receive any surgery throughout the model time frame
- The onset of treatment benefit (i.e., tremor relief) differs based on surgery type.⁴⁹ The benefit of MRgFUS neurosurgery and radiofrequency thalamotomy appears right away. The benefit of deep brain stimulation appears about 1 month following the procedure, as it takes time to program and optimize the device settings (in-person communication, May 25, 2017; telephone communication, May 30 and 31, 2017). Patients continue to experience treatment benefit until tremor recurrence
- Owing to the limited data available on tremor recurrence after surgery, we assume that each patient can have only one recurrence during the model time horizon
- Owing to the lack of clinical evidence on the effectiveness of reoperation, we assume that reoperation will result in the same outcomes as the primary surgery (some with marked improvement, some with mild to moderate improvement)
- There is no disutility associated with reoperation
- Patients who undergo reoperation receive the same surgical procedure as their first procedure
- Patient quality of life returns to baseline (i.e., that associated with disabling tremor) when tremor recurs
- Patients have the same mortality rate as that of the general population^{38,63}

Clinical Parameters

We populated the model with a number of clinical parameters:

- Proportion of patients with marked or mild to moderate improvement following each surgery
- Probability of recurrence
- Probability of reoperation
- Probability of death
- Probability of experiencing adverse effects or complications

Natural History and Treatment Effect

Improvement Post-surgery

In the 2016 randomized controlled trial by Elias et al,³⁸ 3 months after MRgFUS thalamotomy, 27 patients (53%) experienced marked improvement (50–100% improvement), 24 (47%) experienced mild to moderate improvement (10–50% improvement), and 5 (8.9%) experienced no improvement or a worsening of their tremor (less than 10% improvement). These 5 patients were considered to have experienced tremor recurrence (initial improvement but loss of treatment effect by 3 months post-surgery). Based on the literature⁶⁴ and clinical expert opinion (in-person communication, May 23, 2017), tremor relief after thalamotomy that persists for 3 months is nearly always permanent. Therefore, we determined the probability of recurrence to be 8.9% in year 1. Among patients who did not experience tremor recurrence, we considered the proportion of those experiencing marked improvement to be 53%, and the proportion experiencing mild to moderate improvement to be 47%.

For research question 2, we assumed that MRgFUS neurosurgery, radiofrequency thalamotomy, and deep brain stimulation are equally effective, based on the results of a targeted literature review as well as clinical expert opinion. A case-control study of people with essential tremor by Pahwa et al²⁰ found that radiofrequency thalamotomy and deep brain stimulation are equally effective for tremor relief but that radiofrequency thalamotomy is associated with a higher rate of neurological adverse effects. Another retrospective study, by Huss et al,⁴⁰ also showed that unilateral MRgFUS thalamotomy and deep brain stimulation are equally effective. The 2011 American Academy of Neurology guidelines¹⁶ state that there is insufficient evidence to support or refute the superiority of deep brain stimulation or thalamotomy for the treatment of essential tremor. In addition, a randomized controlled trial by Schuurman et al^{21,22} showed that deep brain stimulation and radiofrequency thalamotomy are equally effective in people with medication-refractory, severe tremor owing to Parkinson's disease, multiple sclerosis, or essential tremor.

Very few studies of deep brain stimulation and radiofrequency thalamotomy report the proportion of patients with marked versus mild to moderate improvement. The most commonly reported outcome is percent change in tremor score from baseline. In the 2016 study by Elias et al³⁸ of MRgFUS thalamotomy, the mean score for hand tremor improved by 47% at 3 months. One systematic review identified three studies that reported percent improvement from baseline following deep brain stimulation.¹⁷ In studies in which outcome assessors were not blinded or not reported to be blinded, percent improvement ranged from 65% to 76%.^{65,66} However, a study by Hariz et al,⁶⁷ in which outcome assessors were blinded, reported a percent improvement of 47%, which is similar to that seen with MRgFUS thalamotomy.¹⁷ For radiofrequency thalamotomy, a systematic review by the American Academy of Neurology⁵⁹ found that open-label trials (n = 181) have reported an 80% to 90% tremor reduction following thalamotomy in people with essential tremor. This is also consistent with the findings of the 2016 study of MRgFUS thalamotomy by Elias et al.³⁸

Since there have been no head-to-head clinical trials comparing MRgFUS neurosurgery with deep brain stimulation or radiofrequency thalamotomy, we assumed that each type of surgery results in the same proportions of patients with marked improvement (53%) and mild to moderate improvement (47%). Clinical experts validated this assumption (email communication, July 13, 2017).

Tremor Recurrence

After surgery, some people may initially experience satisfactory tremor relief but experience tremor recurrence within a few months. This could be the result of suboptimal lesion location (for thalamotomy) or lead placement (for deep brain stimulation) owing either to inaccuracy in the stereotactic procedure or to inter-individual anatomic variability in the target.⁶⁸⁻⁷¹ Some people may experience tremor recurrence after several years, potentially as a result of disease progression.^{68,69,72} Recurrence is not well reported in the literature, and its definition varies from study to study, especially with regard to deep brain stimulation. Based on crude estimates in the literature⁷³ and clinical expert opinion (in-person communication, May 23, May 25, and June 19, 2017; telephone communication, May 30 and 31, 2017), the rate of recurrence 5 years following radiofrequency thalamotomy is about 20% to 30%. Since MRgFUS neurosurgery and radiofrequency thalamotomy are both lesional surgeries, we assumed that the recurrence rate would be the same for both procedures in the reference case (confirmed by clinical experts). Therefore, we calculated the annual probability of recurrence in years 2 to 5 to be about 4.7%, assuming the 5-year recurrence rate to be 25% and the year 1 recurrence rate to be 8.9%.

However, since MRgFUS neurosurgery is a new technology and little is known about its long-term efficacy, clinical experts suggested that a larger number of people may experience tremor recurrence over a longer follow-up time, possibly 50% over 5 years (email communication, July 13, 2017). We considered this possibility in our sensitivity analysis.

According to the literature⁶⁴ and clinical expert opinion (email communication, July 13, 2017), tremor recurrence following deep brain stimulation can nearly always be controlled by adjusting the stimulation level of the device (reprogramming) and therefore does not require reoperation. As a result, we assumed the probability of tremor recurrence following deep brain stimulation to be 0%.

Reoperation After Tremor Recurrence

Owing to resource limitations (e.g., wait list) and/or patient preferences, not all people whose tremor recurs following surgery will undergo reoperation. Following Elias et al (2016),³⁸ we estimated that 40% of people who undergo either MRgFUS neurosurgery or radiofrequency thalamotomy may undergo a second surgery once tremor recurs.

As a result of a lack of clinical evidence on the effectiveness of reoperation, we assumed the second operation would result in the same possibility of outcomes as the primary surgery (53% with marked improvement and 47% with mild to moderate improvement).

Table 23 presents the clinical effectiveness parameters used in the economic model.

Table 23: Clinical Effectiveness Parameters Used in the Economic Model

Parameter	Value	Assumption	Source
Improvement Post-surgery (DBS, MRgFUS, RF)			
Percentage of patients with marked improvement	53%	DBS, MRgFUS, and RF are equally effective	Elias et al, 2016 ³⁸ ; expert opinion
Percentage of patients with mild to moderate improvement	47%		
Probability of Recurrence ^a (MRgFUS, RF)			
Year 1	8.9%	MRgFUS and RF have the same recurrence rate; calculation based on a 5-year recurrence rate of 25%	Elias et al, 2016 ³⁸ ; expert opinion
Years 2–5	4.7%		Hirai et al, 1983 ⁷³ ; expert opinion
Probability of Recurrence ^a (DBS)			
Years 1–5	0%	Tremor recurrence following DBS can be controlled by adjusting the stimulation level of the device (reprogramming) and does not require reoperation	Tasker et al, 1998 ⁶⁴ ; expert opinion
Probability of Reoperation After Recurrence (MRgFUS or RF)			
Years 1–5	40%	The probability of reoperation is the same for MRgFUS and RF	Elias et al, 2016 ³⁸

Abbreviations: DBS, deep brain stimulation; MRgFUS, magnetic resonance-guided focused ultrasound; RF, radiofrequency thalamotomy.

^aRecurrence refers to diminished tremor control to the point of requiring reoperation.

Mortality

The literature^{38,63} and clinical experts generally suggest that essential tremor does not affect life expectancy (in-person communication, May 25 and June 19, 2017; telephone communication, May 30 and 31, 2017). Therefore, we assumed people with essential tremor have the same mortality rate as the general population.^{38,63} We obtained the annual probability of all-cause natural mortality from Statistics Canada life tables for 2009 to 2011.^{74,75}

Based on the literature^{38,63} and clinical expert opinion (in-person communication, May 25 and June 19, 2017; telephone communication, May 30 and 31, 2017), the overall mortality resulting from any surgical complication is very small. A small proportion of people may experience intracranial hemorrhage following open surgery (e.g., radiofrequency thalamotomy or deep brain stimulation). However, according to the literature,²⁰ most intracranial hemorrhage events are asymptomatic, and those that are symptomatic usually resolve over time and do not lead to death. Therefore, we did not consider any surgery-related mortality risk.

Treatment-Related Adverse Effects and Complications

In our analysis, we considered the cost and quality-of-life impact of key adverse effects and complications associated with treatment (Table 24). We included those that are frequent (occurring in $\geq 5\%$ of people), severe, expensive to treat, or have a large impact on a person's health-related quality of life. We excluded those with a negligible impact on health effects or resources from the analysis. We considered adverse effects persisting for more than 1 year after surgery to be long term.

For MRgFUS neurosurgery, we obtained the proportion of people experiencing adverse effects and complications from the 2016 study of MRgFUS thalamotomy by Elias et al.³⁸ Most adverse effects associated with MRgFUS thalamotomy were categorized as mild or moderate.³⁸ The most common adverse effects were gait disturbance (36%) and paresthesia or numbness (38%), which persisted in 9% and 14% of people at 1 year, respectively.³⁸ Transient speech problems (dysarthria and dysphagia) were reported in 4% of people. Headache was reported in 14% of people.³⁸

For radiofrequency thalamotomy and deep brain stimulation, we obtained rates of adverse effects and complications (i.e., adverse events) from a targeted search of published systematic reviews. There are some limitations with the available evidence. The majority of studies included in these systematic reviews are noncomparative case series and case reports. It is also difficult to summarize adverse event rates from these studies, as there are large variations in study design and reporting (e.g., definition of adverse events, whether an event is temporary or permanent, duration of follow-up, and consequences of the events). We thus obtained adverse event rates from published systematic reviews when possible; when not possible, we obtained this information from selected studies based on the following criteria: larger sample sizes, long-term follow-up, reporting of average follow-up time, and reporting of adverse event consequences. We validated these adverse event rates with clinical experts.

Possible adverse effects following radiofrequency thalamotomy include paresthesia, dysarthria, gait disorder, and ataxia.⁷⁶ These adverse effects usually resolve over time, although speech difficulties may persist in some people.⁷⁶ For simplicity, we assumed that radiofrequency thalamotomy and MRgFUS neurosurgery have similar short- and long-term neurological adverse effects (i.e., gait disturbance, paresthesia or numbness), since both are lesional surgeries. Because radiofrequency thalamotomy is an invasive procedure, it is associated with

surgical complications such as infection (2%) and intracranial hemorrhage (1%); these rates are based on expert opinion (telephone communication, May 31, 2017). We obtained the incidence of speech disorders (4.5%) in people with essential tremor undergoing thalamotomy from a systematic review and meta-analysis.²⁷

The adverse effects and complications of deep brain stimulation are often classified into three categories: stimulation related, procedure related, and hardware related.⁶⁰ Common stimulation-related adverse effects include paresthesia, dysarthria, and headache.¹⁷ These are usually mild and short-lived and may resolve after reprogramming the device.^{17,20} Therefore, we did not consider the negative quality-of-life impact caused by stimulation-related adverse effects; we captured only the cost impact as part of the reprogramming visits (see Ongoing Costs section). Similar to radiofrequency thalamotomy, deep brain stimulation is associated with procedure-related complications such as intracranial hemorrhage (0.5%–2.0%) and infection (1–3%).^{61,77,78} There are also deep brain stimulation–specific hardware-related complications, such as lead migration and fracture (1–3%), and device malfunction requiring surgical correction (1–3%).^{61,79}

The rates of procedure- and hardware-related complications vary widely among studies and centers for several reasons^{80,81}:

- Varying definitions of adverse effects and complications
- Varying follow-up times
- Differences in patient selection or number of patients included
- Changes in hardware over time
- Variation in local practice (e.g., surgeon experience, surgical technique, use of prophylactic antibiotics)

Because of this variability, we tested a range of procedure- and hardware-related complication rates in sensitivity analyses to assess the impact of these parameters on the cost-effectiveness results.

Table 24: Treatment-Related Adverse Effects and Complications Included in the Economic Model

Adverse Effect or Complication	Proportion of Patients	Source	Average Duration	Source
MRgFUS Neurosurgery				
1 year post-surgery				
Gait disturbance	27%	Elias et al, 2016 ³⁸	2.8 months	Elias et al, 2016 ³⁸
Paresthesia or numbness	24%	Elias et al, 2016 ³⁸	4.3 months	Elias et al, 2016 ³⁸
Headache	14%	Elias et al, 2016 ³⁸	1.8 months	Elias et al, 2016 ³⁸
Speech problem ^a	4%	Elias et al, 2016 ³⁸	6 months	Elias et al, 2016 ³⁸
Permanent				
Paresthesia or numbness	14%	Elias et al, 2016 ³⁸	Permanent	Elias et al, 2016 ³⁸
Gait disturbance	9%	Elias et al, 2016 ³⁸	Permanent	Elias et al, 2016 ³⁸
Radiofrequency Thalamotomy				
1 year post-surgery				
Gait disturbance	27%	Assume same as MRgFUS	2.8 months	Assume same as MRgFUS
Paresthesia or numbness	24%	Assume same as MRgFUS	4.3 months	Assume same as MRgFUS
Infection	2%	Expert opinion	1 month	Bjerknes et al, 2014 ⁸⁰ , expert opinion
Intracranial hemorrhage	1%	Expert opinion	1 month	Pahwa et al, 2001 ²⁰
Permanent				
Paresthesia or numbness	14%	Assume same as MRgFUS	Permanent	Assume same as MRgFUS
Gait disturbance	9%	Assume same as MRgFUS	Permanent	Assume same as MRgFUS
Speech problem ^a	4.5%	Alomar et al, 2017 ²⁷	Permanent	Zesiewicz et al, 2013 ⁷⁶

Adverse Effect or Complication	Proportion of Patients	Source	Average Duration	Source
Deep Brain Stimulation				
1 year post-surgery, procedure related				
Infection	2%	Fishman et al, 2017 ⁶¹	1 month	Bjerknes et al, 2014 ⁸⁰ ; expert opinion
Intracranial hemorrhage	1%	Fishman et al, 2017 ⁶¹	1 month	Pahwa et al, 2001 ²⁰
Hardware related				
Device malfunction	2%	Fishman et al, 2017 ⁶¹	1 month	Assume same as infection
Lead fracture	2%	Fishman et al, 2017 ⁶¹	1 month	Assume same as infection
Stimulation related^b				
Paresthesia, tingling	19.5%	Flora et al, 2010 ¹⁷	Temporary; resolvable by reprogramming	Flora et al, 2010 ¹⁷ ; Pahwa et al, 2001 ²⁰
Speech problem ^a	15.2% ^c	Alomar et al, 2017 ²⁷	Temporary; resolvable by reprogramming	Flora et al, 2010 ¹⁷ ; Pahwa et al, 2001 ²⁰
Disequilibrium, gait, incoordination, motor disturbance	8.1%	Flora et al, 2010 ¹⁷	Temporary; resolvable by reprogramming	Flora et al, 2010 ¹⁷ ; Pahwa et al, 2001 ²⁰
Headache	7.2%	Flora et al, 2010 ¹⁷	Temporary; resolvable by reprogramming	Flora et al, 2010 ¹⁷ ; Pahwa et al, 2001 ²⁰

Abbreviation: MRgFUS, magnetic resonance-guided focused ultrasound.

^aThe category of "speech problem" includes adverse effects such as hypophonia, dysarthria, aphasia/dysphasia, and dysphagia.

^bFor deep brain stimulation–related adverse effects, we considered only the cost implications and not the quality-of-life impact because these events are short-lived and resolve after reprogramming.

^cWeighted average: 15.2% = 12.3% x 90% (unilateral deep brain stimulation) + 41.4% x 10% (bilateral deep brain stimulation).

Health State Utility Parameters

We obtained health state utility values (Table 25) from a targeted literature search of MEDLINE performed on April 11, 2017, of studies published from inception to the search date. We based the search on the clinical search strategy and applied a methodological filter⁸² to limit retrieval to health state utility values. See Appendix 1 for the literature search strategies, including all search terms.

We found only one study, Herceg et al,⁸³ that measured utility using the European Quality of Life—5 Dimensions (EQ-5D) instrument in people with disabling essential tremor. Although essential tremor is a common movement disorder, studies that report utility values for this condition are sparse. Most studies we found employed either disease-specific questionnaires (e.g., QUEST or a modified version of the Parkinson's Disease Questionnaire) or non-preference-based instruments (e.g., Nottingham Health Profile, Sickness Impact Profile). For example, the 2016 phase III randomized controlled trial of MRgFUS thalamotomy by Elias et al¹³⁸ assessed quality of life before and after MRgFUS thalamotomy using the QUEST questionnaire. However, these non-preference-based quality-of-life data do not provide a single summary score for a given health state and thus cannot be used directly for economic modelling. We were also unable to identify any mapping algorithm that could convert these various quality-of-life measures (e.g., QUEST) into utility values. Appendix 5 provides a summary of the utility search results.

We decided to use utility values from Herceg et al⁸³ because the patient population and health states measured are similar to our model population and health states. Based on this study, we assumed that people with disabling essential tremor have a utility (quality of life) of 0.69, and that people with marked improvement after surgery have a utility of 0.91. For those with mild to moderate improvement after surgery, we assumed a utility of 0.80: half-way between 0.69 and 0.91 ($[0.69 + 0.91] \div 2 = 0.80$). Following tremor recurrence, we assumed that a person's utility would return to baseline. The utility following reoperation would be 0.91 for marked improvement and 0.80 for mild to moderate improvement. We also included a decrease in quality of life owing to treatment-related adverse effects or complications. Table 25 summarizes the utility values we extracted from the literature.

Table 25: Health State Utility Parameters Used in the Economic Model

	Mean Utility	Standard Deviation	Sample Size	Source
Health State				
Alive with disabling tremor (baseline)	0.69	0.30	24	Herceg et al, 2012 ⁸³
Improved tremor, post-surgery (marked improvement)	0.91	0.08	24	Herceg et al, 2012 ⁸³
Improved tremor, post-surgery (mild to moderate improvement)	0.80	—	—	Assumption: calculated as the average of baseline and marked improvement post-surgery
Tremor recurrence, no reoperation	0.69	0.30	24	Assumption: quality of life returns to baseline
Tremor recurrence, reoperation (marked improvement)	0.91	—	—	Assumption: same as no recurrence, marked improvement
Tremor recurrence, reoperation (mild to moderate improvement)	0.80	—	—	Assumption: same as no recurrence, mild to moderate improvement
Adverse Effect or Complication				
Gait disturbance	0.82	—	—	Yardley et al, 2012 ⁸⁴
Paresthesia or numbness	0.81	—	—	Thoma et al, 2006 ⁸⁵
Speech disorder	0.54	—	—	Tengs et al, 2000 ⁸⁶
Headache	0.77	—	—	Tengs et al, 2000 ⁸⁶
Infection	0.64	—	—	Lee et al, 2010 ⁸⁷ ; Gheorghe et al, 2015 ⁸⁸
Intracranial hemorrhage	0.60	—	—	Lenert et al, 1997 ⁸⁹
Lead fracture or device malfunction	0.66	—	—	Gada et al, 2012 ⁹⁰

Cost Parameters

We included the following costs in our model:

- Diagnostic and imaging tests
- Professional fees (e.g., neurologist, neurosurgeon, MRI technician, nurse, surgical assistant, anesthesiologist)
- Procedure (including deep brain stimulation device)
- Long-term monitoring
- Medications for essential tremor
- Managing adverse effects and complications

We obtained cost inputs from standard Ontario sources and the published literature. The fees for professional visits, procedures, and consultations were obtained from the Ontario Schedule of Benefits for Physician Services.⁹¹ Hospitalization costs were obtained from the Ontario Case Costing database of the Ministry of Health and Long-Term Care.⁹² Diagnostic and laboratory fees were obtained from the Ontario Schedule of Benefits for Laboratory Services.⁹³ Drug costs were obtained from the Ontario Drug Benefit Formulary.⁹⁴ Costs related to the maintenance and operation of the equipment used in MRgFUS neurosurgery were obtained from clinical experts

and the manufacturer (in-person communication, May 25 and June 19, 2017; telephone communication, May 30 and 31, 2017).

We report all costs in 2017 Canadian dollars. Where 2017 costs were unavailable, we used the health care component of the Statistics Canada Consumer Price Index (CPI) to adjust costs to 2017 Canadian dollars (2017 CPI = 125.7; 2015 CPI = 123.1; 2016 CPI = 124.7).³⁰ We describe our costing methods in detail below.

No Surgery

According to clinical experts (in-person communication, May 23 and 25, 2017), patients who do not undergo surgery usually receive both propranolol and primidone (at a cost of \$269 per year; Table 26). We obtained average daily doses from the literature^{76,95,96} and unit costs for the drugs from the Ontario Drug Benefit Formulary.⁹⁴ Patients are also typically monitored annually by a neurologist for disease progression (\$176 for a neurology consultation⁹¹).

Table 26: Essential Tremor Medication Costs

Drug	Dose Range, mg/day	Average Dose, mg/day	Unit Cost, \$/mg	Daily Cost, \$	Annual Cost, \$
Propranolol	60–320	185	0.0031	0.57	207
Primidone	50–1,000	482	0.0004	0.17	62
Average cost per year					269

Source: Gironell et al, 2009⁹⁵; Schneider et al, 2014⁹⁶; Zesiewicz et al, 2013.⁷⁶

Surgery

Table 27 summarizes the cost inputs for all surgical procedures. The total mean costs per procedure are \$19,786 for MRgFUS neurosurgery, \$37,377 for deep brain stimulation, and \$11,774 for radiofrequency thalamotomy.

Table 27: Average Surgical Procedure Costs

Resource Item	MRgFUS Neurosurgery, \$	Deep Brain Stimulation, \$	Radiofrequency Thalamotomy, \$	Data Source and Comments
Pre-procedure				
Neurology consultation	176	176	176	Schedule of Benefits (A185) ⁹¹
Neurosurgery consultation	121	121	121	Schedule of Benefits (A045) ⁹¹
MRI scan				
Professional fee	73	73	73	Schedule of Benefits (X421) ⁹¹
Procedure cost	972	972	972	OCC 2015 (CCI code 3.AN.40), ambulatory ⁹²
CT scan				
Professional fee	65	NA	NA	Schedule of Benefits (X401) ⁹¹
Procedure cost	513	NA	NA	OCC 2015 (CCI code 3.AN.20), ambulatory ⁹²
Total pre-procedure costs	1,921	1,343	1,343	
Peri-procedure				
Inpatient procedure cost	14,095 ^a	17,221 ^b	6,822 ^c	MRgFUS thalamotomy (clinical expert, email communication, June 21, 2017); deep brain stimulation (OCC 2015 ⁹²); radiofrequency thalamotomy (OCC 2016 ⁹²)
Device cost	NA	14,355	NA	Medtronic 2011; 90% unilateral DBS based on expert opinion (email communication, July 13, 2017)
Physician fees	1,551	1,551	1,551	Schedule of Benefits (N124) ⁹¹
Surgical assistant	445	590	373	Schedule of Benefits (N124) ⁹¹ (see Appendix 6, Table A8)
Anesthesiologist	585	766	495	Schedule of Benefits (N124) ⁹¹ (see Appendix 6, Table A9)
Total peri-procedure costs	16,677	34,483	9,242	

Resource Item	MRgFUS Neurosurgery, \$	Deep Brain Stimulation, \$	Radiofrequency Thalamotomy, \$	Data Source and Comments
Post-procedure				
MRI scan				
Professional fee	73	73	73	Schedule of Benefits (X421) ⁹¹
Procedure cost	972	972	972	OCC 2015 (CCI code 3.AN.40.^^), ambulatory ⁹²
Neurology, repeat consultation	85	85	85	Schedule of Benefits (A186) ⁹¹
Neurosurgeon, repeat consultation	58	58	58	Schedule of Benefits (A046) ⁹¹
Initial DBS programming	NA	363	NA	Schedule of Benefits (G547, G549) ⁹¹ ; 1.8 visits for initial programming based on Ondo et al, 2005, ⁹⁷ and Picillo et al, 2016 ⁹⁸
Total post-procedure costs	1,189	1,551	1,189	
Total cost per procedure	19,786	37,377	11,774	

Abbreviations: CCI, Canadian Classification of Health Interventions; CT, computerized tomography; MRgFUS, magnetic resonance-guided focused ultrasound; MRI, magnetic resonance imaging; NA, not applicable; OCC, Ontario Case Costing database.

Note: All costs are presented in 2017 Canadian dollars.

^aThis is the operational cost only; capital costs (i.e., those related to equipment, installation, and maintenance) are excluded in the reference case analysis.

^bCCI procedure code 1AE53SEJA (implantation, thalamus and basal ganglia, of electrodes [e.g., recording, stimulating] using burr hole approach) for essential tremor (G250); inflated from 2015 to 2017.

^cCCI procedure code 1AE59SEAW (destruction, thalamus and basal ganglia, using burr hole approach and radiofrequency probe) for all diagnoses; inflated from 2016 to 2017.

Pre-procedure Costs

Before each surgery, we assumed that patients would receive two consultations: one each by a neurologist and a neurosurgeon. Further, we assumed patients would undergo an MRI scan to identify the target location. For MRgFUS neurosurgery, an additional CT scan is needed to measure the thickness of the skull. Therefore, we estimated the total mean preoperative costs to be \$1,921 for MRgFUS neurosurgery, \$1,343 for deep brain stimulation, and \$1,343 for radiofrequency thalamotomy (see Table 27).

Peri-procedure Costs

MRgFUS Neurosurgery

We estimated the inpatient procedure cost of MRgFUS neurosurgery through consultation with clinical experts (email communication, June 21, 2017) and an MRgFUS device manufacturer (in-person communication, June 19, 2017) (Table 28). We excluded the capital and fixed costs (i.e., equipment, installation, and maintenance costs) of the MRgFUS system in the reference case analyses since the equipment is already in place (either donated to or purchased by the hospital) at the two centres currently providing MRgFUS neurosurgery in Ontario. Since MRgFUS neurosurgery is a highly specialized procedure, we assumed that if it were to be publicly funded, it would most likely take place in these two centres. In this case, the Ministry of Health and Long-Term Care would be providing funding only for operational costs.

We estimated the operational (variable) cost to be about \$14,095 per case; this cost includes the procedure costs related to medical imaging, other diagnostic procedures, post-procedure recovery (mainly nursing), and other support services (e.g., pharmacy, nutrition, respiratory therapy). In a scenario analysis, we reduced the operational cost to \$10,095 per case, considering the possibility that hospitals may send patients home on the same day as the surgery. In this case, some post-procedure recovery costs can be avoided, and the variable cost can be reduced by \$4,000 per case.

We considered the full cost of MRgFUS neurosurgery (including both fixed and variable costs) in another scenario analysis. We estimated the total fixed cost per year to be \$461,000; this cost consists of the equipment cost, annual service contract, and salary of a full-time coordinator (employed only once there are 100 cases per year). We then divided this amount by an annual case load of 24 (the current level) to derive an average fixed cost of \$19,208 per case. Therefore, if the annual case load remains 24 patients per year, the full cost per MRgFUS procedure would be \$33,303 (\$19,208 + \$14,095).

We did not include the cost of training medical personnel to use the MRgFUS technology since this training is provided by the manufacturer at no extra cost. We did include the professional fees for a neurosurgeon (\$1,551), surgical assistant (\$445), and anaesthesiologist (\$585) (see Table 27).

Table 28: Inpatient Procedure Costs—MRgFUS Neurosurgery

Resource Item	Cost, \$
Insightec system and equipment	1,950,000
Installation	180,000
Capital/Fixed Costs	
Equipment depreciation per year	336,000
Annual service contract	125,000
Full-time coordinator (\$100,000 if 100 cases per year)	0
Total fixed cost per year	461,000
Annual case load (current level)	24
Average fixed cost per case	19,208
Operational/Variable Costs	
Procedure costs, including labour and materials (e.g., medical imaging)	7,147
Other diagnostic procedures	404
Post-procedure recovery costs (mainly nursing)	4,822
Other support services (e.g., pharmacy, nutrition, respiratory therapy)	1,722
Total variable cost per case, used for reference case analysis	14,095
Full cost per case (fixed + variable), used for scenario analysis	33,303

Abbreviation: MRgFUS, magnetic resonance-guided focused ultrasound.
 Note: All costs are presented in 2017 Canadian dollars.

Deep Brain Stimulation

According to the Ontario Case Costing database, the hospital cost of deep brain stimulation is \$16,865 per procedure (standard deviation [SD]: \$2,980, in 2015 CAD), with an average length of stay of 1.4 days. A unilateral deep brain stimulation device costs about \$13,649, and a bilateral device costs about \$20,709 (Appendix 6, Table A7). According to clinical expert opinion (email communication, July 13, 2017), about 90% of patients who undergo deep brain stimulation have a unilateral procedure; thus, we estimated the average cost of deep brain stimulation to be \$14,355. In the reference case analysis, we assumed that Medtronic's Activa SC (single-channel) and PC (double-channel) systems are the most commonly used deep brain stimulation devices. The battery of the implantable pulse generator generally lasts 5 to 7 years, at which point it must be replaced at an additional cost.⁹⁹ We also included the professional fees for a neurosurgeon (\$1,551), surgical assistant (\$590), and anaesthesiologist (\$766) (see Table 27).

Radiofrequency Thalamotomy

According to the Ontario Case Costing database, the hospital cost of radiofrequency thalamotomy is \$6,768 per procedure (SD: \$5,099, in 2016 CAD), with an average length of stay of 1.4 days. We also included the professional fees for neurosurgeon (\$1,551), surgical assistant (\$373), and anaesthesiologist (\$495) (see Table 27).

Post-procedure Costs

MRgFUS Neurosurgery and Radiofrequency Thalamotomy

We assumed that after MRgFUS neurosurgery or radiofrequency thalamotomy, a patient would receive one repeat consultation with a neurosurgeon (\$58) and one from a neurologist (\$85). We also assumed one follow-up MRI scan to check the location of the lesion.

Deep Brain Stimulation

We assumed that after deep brain stimulation, a patient would receive one repeat consultation with a neurologist and one from a neurosurgeon (to check the patient's condition and incisions),⁹⁹ as well as an average of 1.8 visits for initial device programming.⁹⁷ This assumption is based on the North American Survey of Placement and Adjustment Strategies for Deep Brain Stimulation⁹⁷ and the Toronto Western Hospital algorithm for deep brain stimulation programming.⁹⁸ Initial device programming is performed in clinic at least 3 weeks after surgery to lessen the impact of the dynamic impedance changes caused by tissue reaction to the electrode placement. After the first programming visit, some patients may come back for a further 1 to 2 appointments to optimize stimulation settings (to maximize tremor control while minimizing stimulation-induced adverse effects). Most patients complete programming in less than 2 months. Clinicians may set a given parameter range and instruct patients how to slowly tune the stimulation at home with the help of a remote control. Therefore, we estimated the total expected postoperative physician reimbursement to be \$506 (\$58 + \$85 + \$363).⁹¹ We also assumed one follow-up MRI scan to check the location of the lesion.

Ongoing Costs

Medication Costs

After surgery, some people may stop taking medication, whereas some may need to continue taking medication to manage residual tremor. According to clinical experts (email communication, July 13, 2017), 50% of people who experience marked improvement after surgery typically reduce the dose of their tremor medication by half (post-surgery cost: \$202 per year); people who experience mild to moderate improvement following surgery tend to remain on the same dose as before surgery (at a cost of \$269 per year) (see Table 26).

Monitoring Costs

According to clinical experts, people who undergo MRgFUS neurosurgery or radiofrequency thalamotomy are monitored annually by a neurologist for disease progression (\$176 per year).⁹¹

People who undergo deep brain stimulation typically have more frequent visits to adjust the stimulation level and/or to check the battery status of the device every 6 to 12 months. The number of visits is estimated to be 6.2 in the first year following surgery and 2.3 in subsequent years.⁹⁷ The cost of a reprogramming session is \$201 (Schedule of Benefits, codes G547 and G549, assuming a rate of 90% unilateral procedures).⁹¹ Therefore, we estimated the monitoring cost of deep brain stimulation to be \$1,249 per patient in the first year and \$463 per patient in subsequent years.

Deep Brain Stimulation Device Battery Replacement Costs

For people who have undergone deep brain stimulation, we assumed that reoperation to replace the device battery is needed every 5 years. This procedure is performed on an outpatient basis with local anaesthesia. We estimated the cost of the battery replacement

surgery to be \$11,329 (includes the operating cost of \$2,434 [2009 CAD]¹⁰⁰ and the device cost of \$8,689, assuming a rate of 90% unilateral procedures).

Costs of Reoperation After Tremor Recurrence

For MRgFUS neurosurgery and radiofrequency thalamotomy, the cost of reoperation is the same as the cost of the initial procedure.

Costs of Managing Adverse Effects and Complications

We based the treatment costs for adverse effects and complications on the published literature and clinical expert opinion (see Table 24 and Treatment-Related Adverse Effects and Complications section). The resources used were multiplied by the unit costs to obtain the costs of managing each adverse effect and complication (Table 29).

Table 29: Average Costs of Managing Adverse Effects and Complications

Resource Item	Total Cost, \$	Resources Used (Source)
Short-term adverse effects and complications		
Gait disturbance	108.95	One repeat neurologist visit (assumption); 25% of patients prescribed physical therapy (Elias et al, 2016 ³⁸)
Paresthesia or numbness	84.95	One repeat neurologist visit (assumption)
Speech disorder	84.95	One repeat neurologist visit (assumption)
Headache	84.95	One repeat neurologist visit; over-the-counter pain medication (assumption)
Intracranial hemorrhage	7,634.74	Half of cases symptomatic (assumption; cost of symptomatic intracranial hemorrhage obtained from OCC)
Infection following deep brain stimulation	22,461.04	60% require reoperation; 40% treated as outpatients (Fenoy et al, 2012 ¹⁰¹ ; Fenoy et al, 2014 ⁷⁸)
Infection following radiofrequency thalamotomy	5,591.82	60% treated as inpatients, 40% treated as outpatients (expert opinion)
Permanent adverse effects		
Gait disturbance	0	No treatment required (expert opinion); 20% of patients require a walker (Elias et al, 2016 ³⁸) ^a
Paresthesia or numbness	0	No treatment required (expert opinion)
Speech disorder	0	Speech therapy for some patients (expert opinion) ^a
Deep brain stimulation—hardware-related complications		
Lead fracture or migration	25,111.88	Reoperation to replace the lead (Fenoy et al, 2014 ⁷⁸)
Device malfunction	37,377.05	Reoperation to replace the device (Fenoy et al, 2014 ⁷⁸)

^aWe did not include the costs of assistive devices and speech therapy, as they are usually not covered by public payers.

For deep brain stimulation, to avoid double-counting, we considered the costs of managing stimulation-related adverse effects already captured under the reprogramming visit costs (see Ongoing Costs section).

For intracranial hemorrhage, the literature reports that about half of cases are symptomatic and all symptoms usually resolve within a month.^{20,102} No treatment is needed for asymptomatic intracranial hemorrhage. Patients with symptomatic hemorrhage may be hospitalized. We obtained the cost of hospitalization for intracranial hemorrhage from the Ontario Case Costing database (\$15,148 per case [2016 CAD]).⁹²

The literature and clinical experts report that for infection following deep brain stimulation, 60% of patients must have all device components removed and replaced, whereas 40% can be treated as outpatients with oral antibiotics (cephalexin 500 mg orally every 6 hours) for 1 month.^{78,92,94,101} For infection following radiofrequency thalamotomy, we assumed that 60% of patients would be hospitalized and 40% would be treated with oral antibiotics on an outpatient basis.^{92,94}

Based on the literature and clinical expert opinion, all deep brain stimulation–hardware-related complications require reoperation.⁷⁸ For device malfunction, the entire deep brain stimulation device must be removed and reimplanted. For lead fracture or migration, a reoperation is needed to replace the lead.

Societal Cost

In a scenario analysis, we used a societal perspective and included the following types of costs:

- Out-of-pocket cost (i.e., parking at hospital)
- Cost of travel to receive treatment
- Cost of people's time spent travelling and receiving treatment
- Cost of lost productivity

For out-of-pocket costs, we considered the cost of parking at the hospital. We estimated the number of days patients spent at the hospital and applied a maximum daily parking rate of \$26.⁹² Based on clinical expert opinion (in-person communication, May 23 and 25, 2017; telephone communication, May 30 and 31, 2017), patients undergoing MRgFUS neurosurgery, radiofrequency thalamotomy, and deep brain stimulation stay at the hospital for about 2 days, 3 to 4 days, and 4 to 5 days, respectively.

We estimated the cost of travel to receive treatment by multiplying the average cost per trip by the number of round-trips each year (for physician consultation and annual monitoring, and to the hospital for surgery). We estimated the average cost per round-trip to be about \$10.80.¹⁰³ We obtained the number of programming visits for deep brain stimulation from the literature.⁹⁷

We based people's time spent travelling and receiving treatment on both the literature¹⁰⁴ and expert opinion (in-person communication, May 23 and 25, 2017; telephone communication, May 30 and 31, 2017). According to a Canadian study by Hunka et al,¹⁰⁴ in the first year following deep brain stimulation surgery, the mean total time spent programming the stimulator and assessing a person with essential tremor is about 22.3 hours. To value the time of people undergoing a procedure (the majority of whom are not in the work force), we used the Ontario minimum wage of \$11.60 per hour plus a 30% employee benefit.¹⁰⁵

Last, we considered the cost of lost productivity for people undergoing neurosurgery for essential tremor. The average age of the model population is 71 years, and 7% of people aged 70 years and older are still in the work force according to Statistics Canada.¹⁰⁶ Therefore, we assumed that 7% of the model population are unable to work because of their disease and used the median income in Ontario (\$33,840) to estimate the cost of lost productivity.⁹¹ We did not

consider the lost productivity cost of caregivers since, according to clinical expert opinion (in-person communication, May 23 and 25, 2017; telephone communication, May 30 and 31, 2017), the majority of people with essential tremor do not require caregiver support.

Table 30 presents the societal costs included in the economic model.

Table 10: Societal Costs per Person by Treatment Strategy

	No Surgery	MRgFUS Neurosurgery	Radiofrequency Thalamotomy	Deep Brain Stimulation	Source
Out-of-Pocket Cost (parking)					
Year 1, days spent in hospital	–	2	3.5	4.5	Sunnybrook hospital, 2017 ⁹² ; expert opinion
Year 1, cost	–	\$52.00	\$91.00	\$117.00	
Cost of Travel to Receive Treatment					
Year 1, round-trips	1	5	5	13	Ondo et al, 2005 ⁹⁷ ; expert opinion
Subsequent years, round-trips	1	1	1	2.3	
Year 1, cost	\$10.80	\$54.00	\$54.00	\$140.40	
Subsequent years, cost	\$10.80	\$10.80	\$10.80	\$24.84	
Time Spent Travelling and Receiving Treatment					
Year 1, hours	2	56	92	146.3	Hunka et al, 2005 ¹⁰⁴ ; expert opinion
Subsequent years, hours	2	2	2	4.6	
Year 1, cost	\$30.16	\$844.48	\$1,387.36	\$2,206.20	
Subsequent years, cost	\$30.16	\$30.16	\$30.16	\$69.37	
Lost Productivity					
Cost per year	\$2,369.00	–	–	–	Statistics Canada, 2016 ⁹¹

Analysis

For the reference case analyses (research questions 1 and 2), we performed both deterministic and probabilistic analyses. We calculated the deterministic results using the best point estimates for each parameter. We conducted the probabilistic analysis by running 5,000 Monte Carlo simulations to capture parameter uncertainty. When possible, we specified distributions around input parameters using the mean and standard deviation. Costs were characterized by gamma distributions, and probabilities and utilities were characterized by beta distributions. If not specified, other parameters were assumed fixed. See Appendix 7, Table A10, for a list of the model variables and their corresponding distributions.

We determined the costs and quality-adjusted life-years (QALYs) for each treatment and calculated the incremental cost-effectiveness ratio (ICER) of MRgFUS neurosurgery compared with other treatments. We also assessed the probability of each treatment being cost-effective over a range of thresholds.

We conducted deterministic sensitivity analyses (e.g., changing from the mean to the upper and lower limits of the 95% confidence interval of the variables) to assess the impact of key

variables on the ICER. We also conducted several scenario analyses related to methodological and structural uncertainty. These are summarized in Table 31.

Table 31: Scenario Analyses

Parameter	Parameter/Assumption Used in Reference Case	Parameter/Assumption Used in Scenario Analysis
Cost perspective	Public payer (Ontario Ministry of Health and Long-Term Care)	Societal
Time horizon	5 years	1 year; 10 years
Capital cost of MRgFUS neurosurgery	Excluded (inpatient procedure cost of MRgFUS neurosurgery: \$14,095 per case)	Included (inpatient procedure cost of MRgFUS neurosurgery increased to \$33,033 per case)
Post-surgery recovery cost of MRgFUS neurosurgery	Included (inpatient procedure cost of MRgFUS neurosurgery: \$14,095 per case)	Reduced (inpatient procedure cost of MRgFUS neurosurgery reduced to \$10,095 per case)
MRI scan cost	\$972 per scan (based on OCC data ⁹²)	Reduced by one-third to \$324 per scan (based on expert opinion)
Probability of recurrence over 5 years for MRgFUS neurosurgery	25% (based on Hirai et al, 1983 ⁷³ and expert opinion)	50% (based on expert opinion)
Utility of mild to moderate improvement, post-surgery	0.80 (based on Herceg et al, 2012 ⁸³)	0.71 (based on Herceg et al, 2012 ⁸³)
Probability of recurrence in year 1 for MRgFUS neurosurgery and radiofrequency thalamotomy	8.9% (based on Elias et al, 2016 ³⁸)	11% (based on Zaaroor et al, 2017 ⁴⁵)
Surgical effectiveness of MRgFUS neurosurgery, radiofrequency thalamotomy, and deep brain stimulation	Same for all surgeries: 53% with marked improvement; 47% with mild to moderate improvement (based on Elias et al, 2016 ³⁸)	MRgFUS neurosurgery: 91.3% with marked improvement (absence of tremor or occasional tremor); 8.7% with mild to moderate improvement (partial tremor) Radiofrequency thalamotomy: 100%; 0% Deep brain stimulation: 89.5%; 10.5% (Based on Kim et al, 2017 ⁴⁶)

Abbreviations: MRgFUS, magnetic resonance-guided focused ultrasound; MRI, magnetic resonance imaging; OCC, Ontario Case Costing database.

We validated our economic evaluation by verifying the Microsoft Excel model and its equations, communicating with clinical experts to ensure the model had face validity, and cross-validating the results with previously published economic evaluations addressing similar decision problems. We also replicated the analysis using a different modelling program (TreeAge Pro). The two models produced the same results.

Generalizability

The findings of this economic analysis cannot be generalized to all people with essential tremor. They may, however, be used to guide decision-making about the specific patient populations addressed in the studies evaluated by Health Quality Ontario.

Expert Consultation

Throughout the development of this model, we consulted with clinical and methodological experts with expertise in neurology, neurosurgery, radiology, and medical imaging, as well as with other specialists, advisors, and clinicians with relevant experience. The role of the expert advisors was to review the structure and inputs of the economic model to confirm that the information we used reasonably reflected the clinical setting. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of the consulted experts.

Results

Research Question 1: MRgFUS Neurosurgery Versus No Surgery in People With Essential Tremor Ineligible for Invasive Neurosurgery

Reference Case Deterministic Analysis

Table 32 presents the results of the deterministic reference case analysis for the comparison of MRgFUS neurosurgery versus no surgery. Over a 5-year time horizon, MRgFUS neurosurgery has a total mean cost of \$23,507 and a total mean of 3.69 QALYs. Compared with no surgery, MRgFUS neurosurgery is associated with an incremental cost of \$21,448 and an incremental QALY of 0.50. The ICER of MRgFUS neurosurgery compared with no surgery is \$43,075 per QALY gained.

Table 32: Deterministic Reference Case Analysis Results—Cost-Effectiveness of MRgFUS Neurosurgery Versus No Surgery

	MRgFUS Neurosurgery	No Surgery
Cost of primary surgery	\$19,786	—
Cost of monitoring	\$814	\$814
Cost of medications	\$1,095	\$1,245
Cost of reoperation	\$1,741	—
Cost of managing adverse events	\$71	—
Total costs	\$23,507	\$2,060
Life-years	4.63	4.63
QALYs	3.69	3.19
Incremental cost	\$21,448	
Incremental life-years	0.00	
Incremental QALYs	0.50	
ICER (cost/QALY)	\$43,075	

Abbreviations: ICER, incremental cost-effectiveness ratio; MRgFUS, magnetic resonance-guided focused ultrasound; QALY, quality-adjusted life-year.

Reference Case Probabilistic Analysis

For the comparison of MRgFUS neurosurgery versus no surgery, the results of the probabilistic reference case analysis were similar to those of the deterministic analysis (Appendix 8, Table A11). Over a 5-year time horizon, MRgFUS neurosurgery has a total mean cost of \$23,497 (95% CI: \$22,044–\$25,287) and a total mean of 3.70 QALYs (95% CI: 3.48–3.89). Compared with no surgery, MRgFUS neurosurgery is associated with an incremental cost of \$21,438

(95% CI: \$19,985–\$23,227) and an incremental quality-adjusted survival of 0.47 QALYs (95% CI: 0.10–0.90). The ICER of MRgFUS neurosurgery compared with no surgery is \$45,817 per QALY gained.

The cost-effectiveness acceptability curve presented in Figure 6 shows the probability of MRgFUS neurosurgery being cost-effective compared with no surgery across a range of willingness-to-pay thresholds. At common willingness-to-pay thresholds of \$50,000 per QALY and \$100,000 per QALY, MRgFUS neurosurgery is 56.0% and 89.5% likely to be cost-effective, respectively.

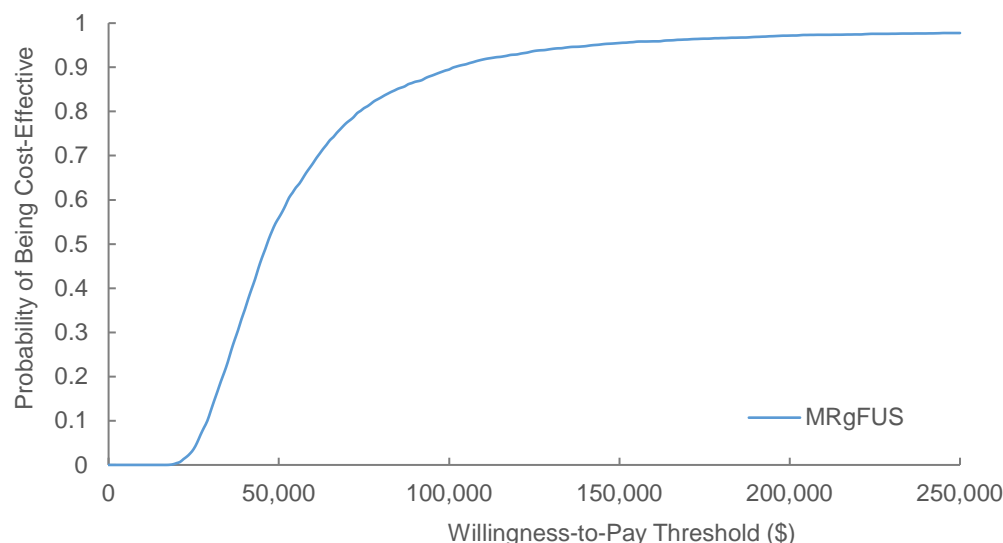


Figure 6: Cost-Effectiveness Acceptability Curve—MRgFUS Neurosurgery Versus No Surgery

Deterministic Sensitivity Analyses

Figure 7 presents a tornado diagram illustrating the results of the deterministic sensitivity analyses. The ICER of MRgFUS neurosurgery compared with no surgery was most sensitive to assumptions regarding baseline utility. When assuming a utility of 0.81 (the upper limit of the 95% confidence interval for baseline utility) for people with disabling tremor, the incremental cost of MRgFUS neurosurgery versus no surgery remains the same, while the incremental effectiveness decreases to 0.10 QALYs, resulting in an ICER of more than \$200,000 per QALY. Our results remained robust when other parameters were varied.

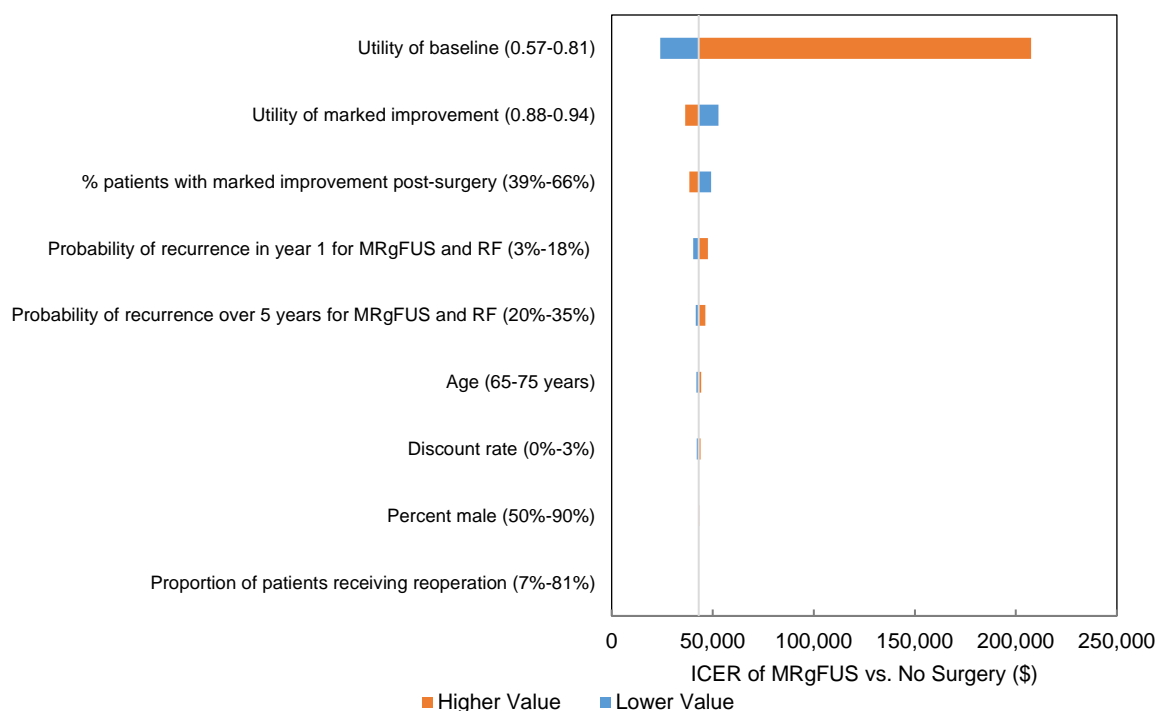


Figure 7: Tornado Diagram—Influence of Key Parameters on the Incremental Cost-Effectiveness Ratio of MRgFUS Neurosurgery Versus No Surgery

Abbreviations: ICER, incremental cost-effectiveness ratio; MRgFUS, magnetic resonance-guided focused ultrasound; RF, radiofrequency

Scenario Analysis

Table 33 presents our scenario analysis results. These results were sensitive to the following model parameters or assumptions: time horizon, inclusion of the capital cost of MRgFUS neurosurgery, utility of people experiencing mild to moderate improvement after surgery, and cost perspective. When the time horizon was shortened to 1 year, the ICER increased to \$241,520 per QALY. When we used a 10-year time horizon, the ICER was reduced by 40% compared to the reference case (\$25,980/QALY). When the capital cost of MRgFUS neurosurgery was included, the ICER almost doubled compared to the reference case (\$85,047/QALY). When we assumed that people would experience only a modest improvement in quality of life following mild to moderate improvement post-surgery (utility of 0.71 vs. 0.80), the ICER became \$65,637 per QALY. When incorporating people's out-of-pocket and lost productivity costs into the reference case analysis, the cost difference between MRgFUS neurosurgery and no surgery was reduced from \$21,448 to \$11,423, resulting in an ICER of \$22,943 per QALY (a reduction of 47% compared to the reference case).

Table 33: Deterministic Scenario Analysis Results—MRgFUS Neurosurgery Versus No Surgery

	MRgFUS Neurosurgery vs. No Surgery		
	Incremental Cost	Incremental QALYs	ICER
Reference case	\$21,448	0.50	\$43,075
Societal perspective	\$11,423	0.50	\$22,943
Time horizon			
1 year	\$20,171	0.08	\$241,520
10 years	\$22,345	0.86	\$25,980
Including capital cost of MRgFUS	\$42,346	0.50	\$85,047
Reducing post-surgery recovery cost of MRgFUS	\$17,096	0.50	\$34,334
Reducing MRI scan cost for all surgeries	\$20,037	0.50	\$40,243
Utility of mild to moderate improvement post-surgery (0.71, based on Herceg et al, 2012 ⁸³)	\$21,448	0.33	\$65,637
Probability of recurrence in year 1 for MRgFUS and RF (11%, based on Zaaroor et al, 2017 ⁴⁵)	\$21,478	0.49	\$43,544
Probability of recurrence over 5 years for MRgFUS (50%, based on expert opinion)	\$23,129	0.45	\$51,965
Surgical effectiveness (based on Kim et al, 2017 ⁴⁶)	\$21,339	0.67	\$31,924

Abbreviations: ICER, incremental cost-effectiveness ratio; MRgFUS, magnetic resonance-guided focused ultrasound; QALY, quality-adjusted life-year; RF, radiofrequency.

Research Question 2: MRgFUS Neurosurgery Versus Radiofrequency Thalamotomy or Deep Brain Stimulation in People With Essential Tremor Eligible for Invasive Neurosurgery

Reference Case Deterministic Analysis

Tables 34 and 35 present the results of the deterministic reference case analysis for the comparison of MRgFUS neurosurgery versus radiofrequency thalamotomy or deep brain stimulation. Over a 5-year time horizon, the total mean costs of MRgFUS neurosurgery, radiofrequency thalamotomy, and deep brain stimulation are \$23,507, \$14,978, and \$57,535, with a total mean of 3.69, 3.61, and 3.94 QALYs, respectively. Radiofrequency thalamotomy is the least costly and least effective procedure, and deep brain stimulation is the most costly and most effective. The ICER of MRgFUS neurosurgery compared with radiofrequency thalamotomy is \$109,795 per QALY gained. The ICER of deep brain stimulation compared with MRgFUS neurosurgery is \$134,259 per QALY gained.

Table 34: Deterministic Reference Case Analysis Results—Cost-Effectiveness of MRgFUS Neurosurgery, Radiofrequency Thalamotomy, and Deep Brain Stimulation

	MRgFUS Neurosurgery	Radiofrequency Thalamotomy	Deep Brain Stimulation
Cost of primary surgery	\$19,786	\$11,774	\$37,377
Cost of monitoring	\$814	\$814	\$3,307
Cost of medications	\$1,095	\$1,095	\$1,081
Cost of reoperation	\$1,741	\$1,036	—
Cost of managing adverse events	\$71	\$259	\$6,307
Cost of battery replacement	—	—	\$9,463
Total cost	\$23,507	\$14,978	\$57,535
Life-years	4.63	4.63	4.63
QALYs	3.69	3.61	3.94

Abbreviations: MRgFUS, magnetic resonance-guided focused ultrasound; QALY, quality-adjusted life-year.

Table 35: Deterministic Reference Case Analysis Results—Incremental Cost-Effectiveness Ratios for MRgFUS Neurosurgery Versus Radiofrequency Thalamotomy or Deep Brain Stimulation

Intervention	Total Mean Cost	Total Mean QALYs	Incremental Cost	Incremental QALYs	Sequential ICER
Radiofrequency thalamotomy	\$14,978	3.61	—	—	—
MRgFUS neurosurgery	\$23,507	3.69	\$8,530 ^a	0.08 ^a	\$109,795 ^a
Deep brain stimulation	\$57,535	3.94	\$34,028 ^b	0.25 ^b	\$134,259 ^b

Abbreviations: ICER, incremental cost-effectiveness ratio; MRgFUS, magnetic resonance-guided focused ultrasound; QALY, quality-adjusted life-year.

^aCompared with radiofrequency thalamotomy.

^bCompared with MRgFUS neurosurgery.

Reference Case Probabilistic Analysis

For the comparison of MRgFUS neurosurgery versus radiofrequency thalamotomy or deep brain stimulation, the results of the probabilistic reference case analysis are similar to those of the deterministic analysis (Appendix 8, Tables A11 and A12). Over a 5-year time horizon, the total mean costs of MRgFUS neurosurgery, radiofrequency thalamotomy, and deep brain stimulation are \$23,497 (95% CI: \$22,044–\$25,287), \$14,972 (95% CI: \$14,096–\$16,051), and \$57,523 (95% CI: \$55,507–\$59,772), with a total mean of 3.70 (95% CI: 3.48–3.89), 3.63 (95% CI: 3.42–3.82), and 3.96 (95% CI: 3.75–4.14) QALYs, respectively. Radiofrequency thalamotomy is the least costly and least effective, and deep brain stimulation is the most costly and most effective. The ICER of MRgFUS neurosurgery compared with radiofrequency thalamotomy is \$119,607 per QALY gained, and the ICER of deep brain stimulation compared with MRgFUS neurosurgery is \$130,850 per QALY gained.

Deterministic Sensitivity Analyses

Figures 8 and 9 present tornado diagrams illustrating the results of the deterministic sensitivity analyses. The ICER of MRgFUS neurosurgery compared with radiofrequency thalamotomy was most sensitive to assumptions regarding the probability of recurrence in the first year following

surgery, the hospital cost of radiofrequency thalamotomy, and the risk of infection related to the radiofrequency thalamotomy procedure (see Figure 8). When the upper limit of the 95% confidence interval for recurrence in year 1 was used (18%), the ICER of MRgFUS neurosurgery versus radiofrequency thalamotomy became \$215,586 per QALY. When assuming a 15% risk of infection for people undergoing radiofrequency thalamotomy, MRgFUS neurosurgery became more cost-effective with an ICER of \$60,307 per QALY.

The ICER of deep brain stimulation versus MRgFUS neurosurgery was sensitive to several assumptions related to deep brain stimulation, such as battery life, onset of benefit, risk of hardware complications, and risk of infection (see Figure 9). When assuming the battery of the deep brain stimulation device can last longer (8–10 years if the device is turned off at night), the ICER of deep brain stimulation versus MRgFUS neurosurgery became smaller (\$96,924/QALY). When assuming a 3-month delay in the onset of treatment benefit with deep brain stimulation, the ICER of deep brain stimulation vs. MRgFUS neurosurgery increased to \$160,560 per QALY. When the risk of hardware complications was doubled (from 4% to 8%), the ICER of deep brain stimulation versus MRgFUS neurosurgery increased to \$160,390 per QALY.

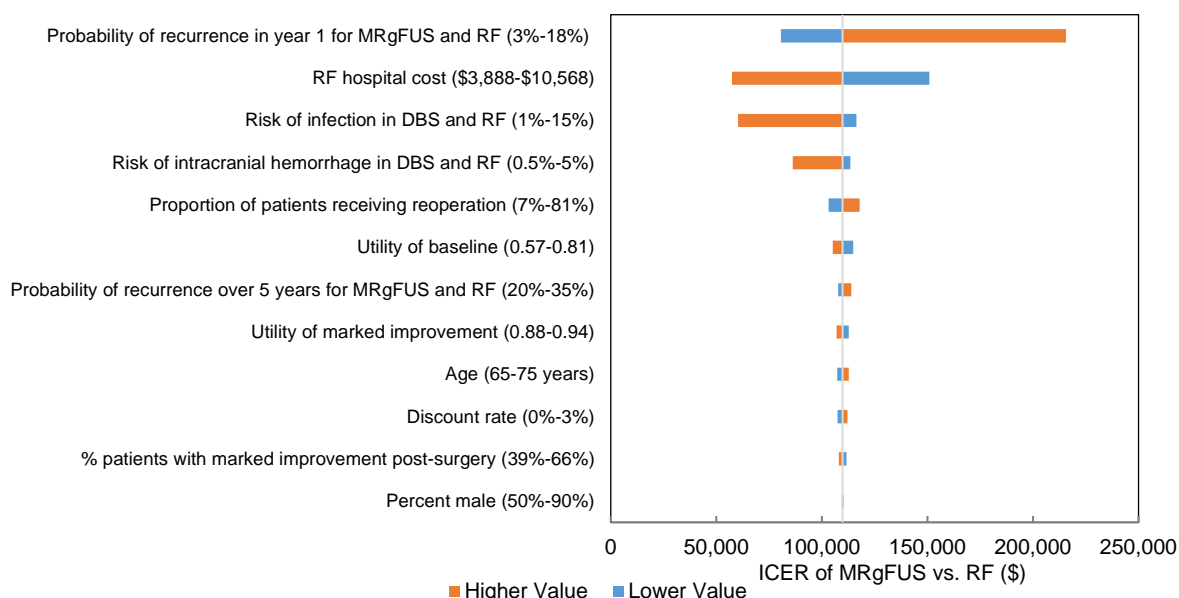


Figure 8: Tornado Diagram—Influence of Key Parameters on the Incremental Cost-Effectiveness Ratio of MRgFUS Neurosurgery Versus Radiofrequency Thalamotomy

Abbreviations: DBS, deep brain stimulation; ICER, incremental cost-effectiveness ratio; MRgFUS, magnetic resonance-guided focused ultrasound; RF, radiofrequency.

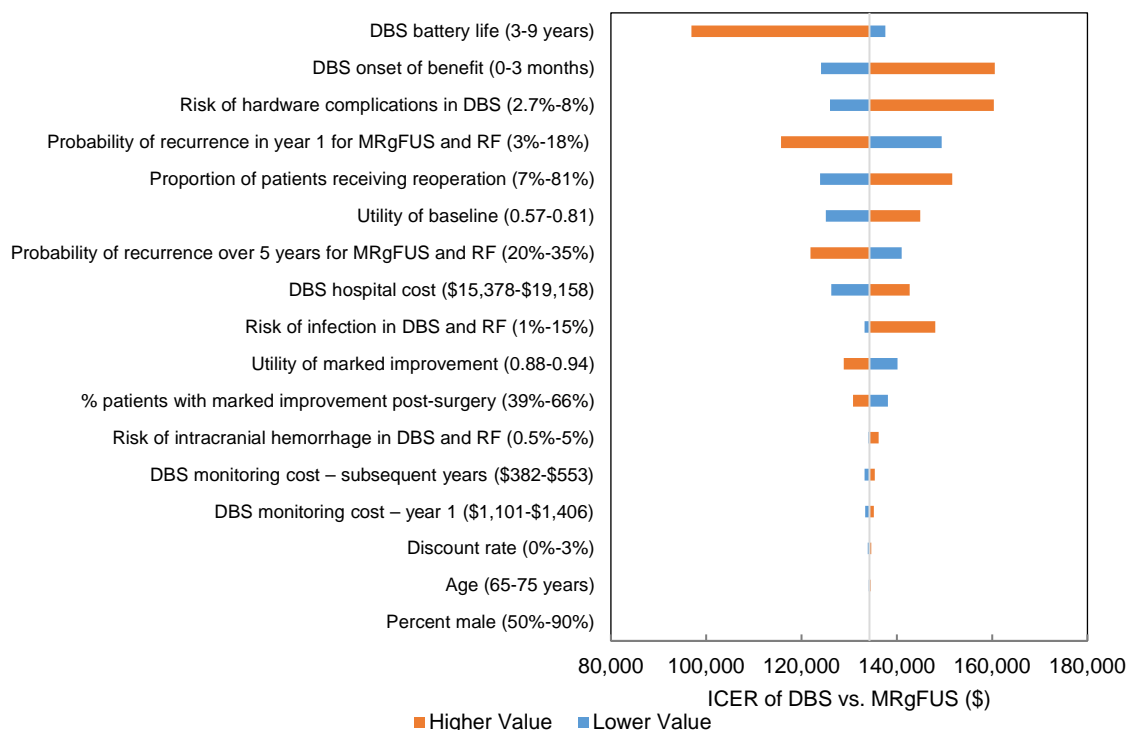


Figure 9: Tornado Diagram—Influence of Key Parameters on the Incremental Cost-Effectiveness Ratio of Deep Brain Stimulation Versus MRgFUS Neurosurgery

Abbreviations: DBS, deep brain stimulation; ICER, incremental cost-effectiveness ratio; MRgFUS, magnetic resonance-guided focused ultrasound; RF, radiofrequency.

Scenario Analysis

Table 36 presents our scenario analysis results. These results were sensitive to time horizon and the inclusion of the capital cost of MRgFUS neurosurgery. When the time horizon was shortened to 1 year, the ICER of MRgFUS neurosurgery versus radiofrequency thalamotomy increased to \$546,289 per QALY, and the ICER of deep brain stimulation versus MRgFUS neurosurgery increased to \$297,776 per QALY. When we used a 10-year time horizon, the ICER of MRgFUS neurosurgery versus radiofrequency thalamotomy decreased to \$63,579 per QALY, and the ICER of deep brain stimulation versus MRgFUS neurosurgery decreased to \$90,486 per QALY. When we included the capital cost of MRgFUS neurosurgery, the ICER of MRgFUS neurosurgery versus radiofrequency thalamotomy increased to \$378,806 per QALY, and the ICER of deep brain stimulation versus MRgFUS neurosurgery was reduced to \$51,803 per QALY. The results did not change much when we applied a societal perspective, since these surgeries are considered to improve people's productivity similarly. When assuming that MRgFUS neurosurgery will have a much higher probability of recurrence over 5 years (50% compared to 25% in the reference case analysis), MRgFUS neurosurgery became less cost-effective compared with radiofrequency thalamotomy, with an ICER of \$410,779 per QALY.

Table 36: Deterministic Scenario Analysis Results—MRgFUS Neurosurgery vs. Radiofrequency Thalamotomy or Deep Brain Stimulation

	MRgFUS vs. RF			DBS vs. MRgFUS		
	Incremental Cost	Incremental QALYs	ICER	Incremental Cost	Incremental QALYs	ICER
Reference case	\$8,530	0.08	\$109,795	\$34,028	0.25	\$134,259
Societal perspective	\$7,948	0.08	\$102,305	\$35,815	0.25	\$141,310
Time horizon						
1 year	\$7,980	0.01	\$546,289	\$19,996	0.07	\$297,776
10 years	\$8,925	0.14	\$63,579	\$45,855	0.51	\$90,486
Including capital cost of MRgFUS	\$29,428	0.08	\$378,806	\$13,129	0.25	\$51,803
Reducing post-surgery recovery cost of MRgFUS	\$4,178	0.08	\$53,775	\$38,380	0.25	\$151,430
Reducing MRI scan cost for all surgeries	\$8,530	0.08	\$109,795	\$33,886	0.25	\$133,702
Utility of mild to moderate improvement post-surgery (0.71, based on Herceg et al, 2012 ⁸³)	\$8,530	0.07	\$115,288	\$34,028	0.23	\$145,485
Probability of recurrence in year 1 for MRgFUS and RF (11%, based on Zaaroor et al, 2017 ⁴⁵)	\$8,541	0.08	\$110,090	\$33,998	0.26	\$131,715
Probability of recurrence over 5 years for MRgFUS (50%, based on expert opinion)	\$10,211	0.02	\$410,779	\$32,346	0.31	\$105,612
Surgical effectiveness (based on Kim et al, 2017 ⁴⁶)	\$8,554	0.04	\$196,484	\$34,023	0.26	\$128,867

Abbreviations: DBS, deep brain stimulation; ICER, incremental cost-effectiveness ratio; MRgFUS, magnetic resonance-guided focused ultrasound; RF, radiofrequency; QALY, quality-adjusted life year.

Discussion

Our reference case analysis showed that in people with essential tremor ineligible for invasive neurosurgery, MRgFUS neurosurgery is cost-effective compared with no surgery (ICER: \$43,075) at commonly used willingness-to-pay thresholds between \$50,000 and \$100,000 per QALY. Our deterministic sensitivity analyses showed that the results are most sensitive to the baseline utility of people with essential tremor (0.69 ± 0.30 [mean \pm SD], based on Herceg et al, 2012,⁸³ using the EQ-5D instrument). When we used the upper limit of the 95% confidence interval for baseline utility, the ICER of MRgFUS neurosurgery versus no surgery increased to more than \$200,000 per QALY. For people who are not as severely affected by the disease, MRgFUS neurosurgery may not be a cost-effective treatment option compared with no surgery. However, essential tremor typically does have a negative impact on people's quality of life. Several studies have found that people with essential tremor have a much poorer quality of life compared with peers without the disease.^{83,107-109} A large Spanish study,⁵⁵ which also used EQ-5D to assess quality of life, reported a utility of 0.73 ± 0.30 (mean \pm SD) in people with essential tremor, which is similar to that of people with other chronic illnesses. We did not use

this study for our reference case analysis since the majority of the participants in the study had mild to moderate disease and were not considered to have medication-refractory disease.

We excluded the capital cost of MRgFUS neurosurgery in the reference case analysis since the two centres currently providing this surgery in Ontario already have the equipment installed, meaning the Ministry of Health and Long-Term Care would be responsible only for the operational costs if MRgFUS neurosurgery becomes publicly funded. Based on expert input, for a variety of reasons (e.g., specialized skill and high capital costs), MRgFUS neurosurgery is probably most feasible to be implemented at a few large centres. If we consider the full cost of MRgFUS neurosurgery (both capital and operational costs, resulting in \$33,303 per case), the ICER almost doubles compared with the reference case (\$85,047/QALY). In another scenario, we lowered the operational cost of MRgFUS neurosurgery by \$4,000 per case, based on expert opinion that hospitals may convert the procedure into a same-day service model. In this case, the ICER of MRgFUS neurosurgery compared with no surgery is reduced to \$34,334 per QALY. However, the likelihood of this reduction occurring will depend on the health condition of people undergoing the procedure and will thus be determined on a case-by-case basis.

Our analysis also showed that in people eligible for invasive neurosurgery, radiofrequency thalamotomy is the least expensive but also least effective treatment option. This is because radiofrequency thalamotomy, as an open surgical procedure, is associated with a risk of intracranial hemorrhage and infection. It is also associated with a higher rate of long-term speech disorders than either MRgFUS neurosurgery or deep brain stimulation. Compared with radiofrequency thalamotomy, MRgFUS neurosurgery is associated with an ICER of \$109,795 per QALY. We found that deep brain stimulation is more effective than radiofrequency thalamotomy and MRgFUS neurosurgery, but it is also more costly. The ICER of deep brain stimulation compared with radiofrequency thalamotomy is \$128,520 per QALY, and the ICER of deep brain stimulation compared with MRgFUS neurosurgery is \$134,259 per QALY.

Deep brain stimulation is currently the surgical standard for moderate to severe, medication-refractory essential tremor. Although no trials have demonstrated the superiority of deep brain stimulation over radiofrequency thalamotomy, deep brain stimulation is the preferred surgical treatment because it is considered reversible and modifiable. In this analysis, we made two assumptions favouring deep brain stimulation: (1) the procedure does not result in tremor recurrence requiring reoperation; and (2) any stimulation-related adverse effects are short-lived and resolvable by reprogramming, thus having no negative impact on the patient's quality of life. However, clinical studies have shown that, in rare cases, people who undergo deep brain stimulation may experience tremor recurrence requiring reoperation.

Both MRgFUS neurosurgery and radiofrequency thalamotomy are good treatment options for people with essential tremor who would have difficulty meeting the follow-up requirements for deep brain stimulation (i.e., for device programming) and for those unable or unwilling to accept the risks associated with an implantable device.⁷⁶ MRgFUS neurosurgery has advantages over both radiofrequency thalamotomy and deep brain stimulation because it is a noninvasive procedure. Thus, it provides a treatment option for people with medication-refractory essential tremor who are ineligible for an invasive procedure. However, MRgFUS neurosurgery is a relatively new technology for which the long-term effectiveness is currently unknown. Therefore, there is some uncertainty as to whether results achieved in the short term will persist. Clinical experts have reported seeing stability in effect up to 2 years following the procedure, and that treatment effects seen at 1 month tend to be stable at 1 year (in-person communication, May 23 and 25, 2017; telephone communication, May 30 and 31, 2017). Although it remains to be demonstrated, some researchers have suggested that outcomes such as durability of effect and

adverse effects owing to suboptimal lesion location may improve over time as centres gain experience with the MRgFUS neurosurgery procedure.

Our primary economic evaluation has several strengths. It is the first economic analysis estimating the economic value of MRgFUS neurosurgery for the treatment of essential tremor in Canada. We assessed the cost-effectiveness of MRgFUS neurosurgery compared with standard treatment in two distinct patient populations: those who are ineligible for invasive neurosurgery and those who are. Our analysis comparing MRgFUS neurosurgery with no surgery in people ineligible for invasive neurosurgery was based on a randomized, double-blinded, placebo-controlled trial,³⁸ a study design considered to provide high-quality evidence. For our analysis comparing MRgFUS neurosurgery with radiofrequency thalamotomy or deep brain stimulation in people eligible for invasive neurosurgery, we assumed that all surgeries are similarly effective but have different safety profiles, based on the literature³⁸ and clinical expert opinion (in-person communication, May 23 and 25, 2017; telephone communication, May 30 and 31, 2017). Our analysis incorporated important long-term clinical outcomes, such as tremor recurrence, reoperation, and permanent or ongoing adverse effects and complications, compared with the study by Ravikumar et al,⁵⁴ which did not include these outcomes.

There were several limitations to our analysis. There is currently no clinical evidence directly comparing MRgFUS neurosurgery with radiofrequency thalamotomy and deep brain stimulation. In the absence of such evidence, we relied on unadjusted comparisons and clinical expert judgment. Owing to a lack of data on the natural history of essential tremor, we were unable to model disease progression by severity. Other than tremor recurrence after the primary surgery, we assumed that in both the “surgery” and “no-surgery” arms of the model, a patient’s condition is stable, since essential tremor is a slowly progressive disorder. Also, we were unable to model quality of life by disease severity, since very few studies have reported utility values for essential tremor. Also, we were unable to use quality-of-life data collected by the randomized controlled trial of MRgFUS thalamotomy³⁸ because there is no mapping algorithm for converting QUEST scores into utility values.

Conclusions

In the subset of people with moderate to severe, medication-refractory essential tremor ineligible for invasive neurosurgery, MRgFUS neurosurgery is a cost-effective treatment option compared with no surgery. Further, as a noninvasive surgical procedure, MRgFUS neurosurgery is a good treatment option for people unable to undergo surgery owing to comorbidities and for those who find the risks of invasive surgery unacceptable. In the subset of people with moderate to severe, medication-refractory essential tremor who are eligible for invasive neurosurgery, MRgFUS neurosurgery is more effective but also more costly than radiofrequency thalamotomy. Compared with the current standard of care, deep brain stimulation, MRgFUS neurosurgery is less expensive but less effective.

BUDGET IMPACT ANALYSIS

Research Question

What is the 5-year budget impact of publicly funding MRgFUS neurosurgery for the treatment of moderate to severe, medication-refractory essential tremor, within the context of the Ontario Ministry of Health and Long-Term Care?

Methods

Target Population

The target population is people with moderate to severe, medication-refractory essential tremor. We estimated the size of the target population based on the published literature^{3,16,110,111} and clinical expert inputs (in-person communication, May 25, 2017; telephone communication, May 30 and 31, 2017). The condition is estimated to affect 4.6% of people 65 years of age and older³; in Ontario, this is about 109,311 people. Of these, an average of 6% seek medical care, and 30% have moderate to severe disease.¹¹⁰ According to the literature^{16,111} and clinical expert opinion (in-person communication, May 25, 2017; telephone communication, May 30 and 31, 2017), of those with no contraindications to drug therapy (99%), 50% will experience a suboptimal response to drugs and/or be unable to tolerate the adverse effects. According to experts, about 85% of these people, around 828 individuals, are eligible for surgery (in-person communication, May 25, 2017; telephone communication, May 30 and 31, 2017). According to the literature^{16,111} and clinical experts (in-person communication, May 25, 2017; telephone communication, May 30 and 31, 2017), for those with contraindications to drugs (1%), it is estimated that 50%, about 10 individuals, are eligible for surgery (less than in the case of those with no contraindications to drugs, since this subpopulation is considered likely to be more fragile and to have comorbidities negatively affecting their surgical risk). Thus, we estimate a total of 838 people with moderate to severe, medication-refractory essential tremor to be eligible for surgery. Table 37 and Figure 10 provide further details on these calculations.

Our estimate is consistent with the number of referrals for MRgFUS neurosurgery received by clinical experts (about 300 referrals from neurologists) (telephone communication, May 18, 2017; in-person communication, May 25, 2017).

Table 37: Epidemiological Inputs Used to Derive Target Population

Parameter	Value	Source
Ontario population aged ≥ 65 years (in 2018)	2,376,327	Ontario Ministry of Finance ¹¹²
Prevalence of essential tremor among those aged ≥ 65 years	4.60%	Louis and Ferreira, 2010 ³
% seeking medical care	6% (0.5–11%)	Louis et al, 1998 ¹¹⁰
% with moderate to severe disease	30%	Expert opinion
% with no contraindications to drug therapy	99%	Expert opinion
% medication refractory or intolerant	50%	Koller et al, 1994 ¹¹¹ ; Zesiewicz et al, 2011 ¹⁶ ; expert opinion
% eligible for surgery (without drug contraindications)	85%	Expert opinion; assumption
% eligible for surgery (with drug contraindications)	50%	Expert opinion

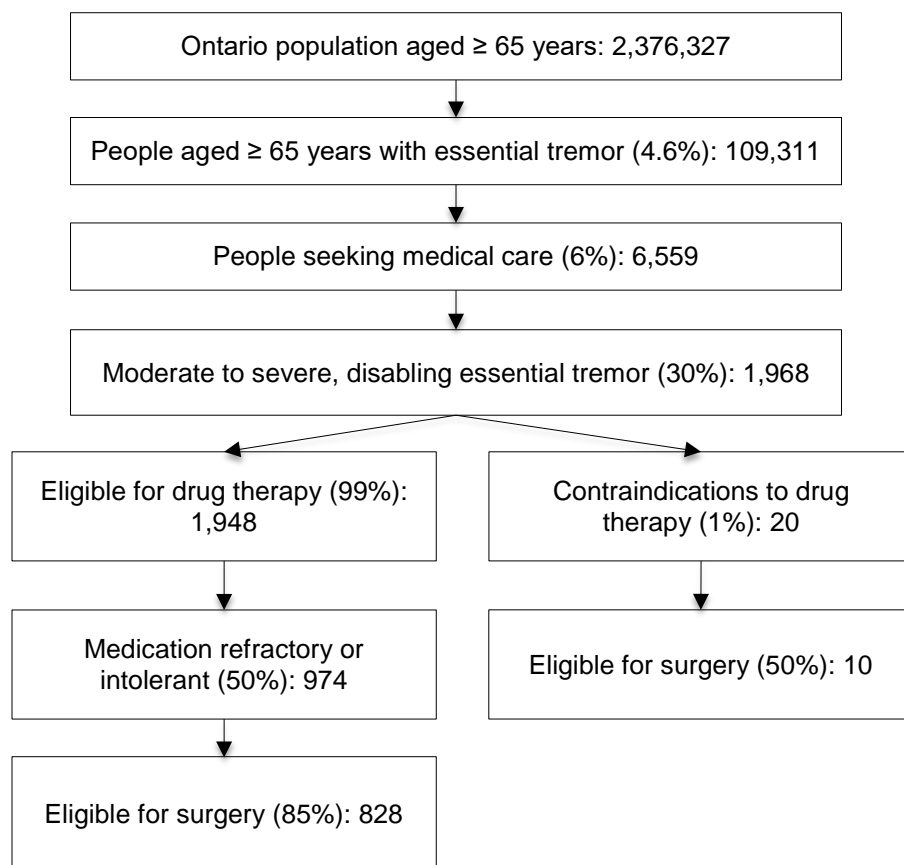


Figure 10: Target Population Estimation

Current Treatment Pattern

Although many people with essential tremor may be eligible for and interested in pursuing surgery, the number of those who actually receive surgery may be much lower owing to factors such as limited resources, referral patterns, limited awareness of treatment options, and aversion to surgery. We obtained the number of thalamotomy and deep brain stimulation procedures performed in Ontario over the past 5 years from the IntelliHealth administrative database (IntelliHealth Ontario, Inpatient Discharges 2012–2016, May 18, 2017) (Table 38). We identified the procedures using the Canadian Classification of Health Intervention codes (1AE) with a diagnosis of essential tremor (ICD-10 code G250). From 2012 to 2016, an average of 14 patients underwent a neurosurgical procedure for essential tremor each year (deep brain stimulation: 60%; Gamma Knife thalamotomy: 30%; radiofrequency thalamotomy: 10%).

Table 38: Number of Deep Brain Stimulation and Thalamotomy Procedures Performed in Ontario, 2012 to 2016

Procedure	CCI Code	Number of Procedures Performed						%
		2012	2013	2014	2015	2016	Average	
Deep brain stimulation	1AE53SEJA; 1AE53SZJA	14	5	12	5	6	8.4	60%
Gamma Knife thalamotomy	1AE27JX	0	2	8	6	5	4.2	30%
Radiofrequency thalamotomy	1AE59SEAW; 1AE59SZAW	1	2	1	3	0	1.4	10%
Total		15	9	21	14	11	14	100%

Abbreviations: CCI, Canadian Classification of Health Intervention.

Source: IntelliHealth Ontario, Inpatient Discharges 2012–2016, May 18, 2017.

From clinical experts, we also know that two centres in Ontario currently treat about two patients per month each with MRgFUS neurosurgery, resulting in 48 MRgFUS neurosurgery procedures per year (telephone communication, May 18, 2017; in-person communication, May 30, 2017). Since this procedure is not currently publicly funded, these patients are not reflected in the administrative databases.

Therefore, the total number of neurosurgical procedures currently performed for the treatment of essential tremor in Ontario per year is 62 (48 with MRgFUS neurosurgery; 14 with deep brain stimulation, Gamma Knife thalamotomy, or radiofrequency thalamotomy).

Uptake of MRgFUS Neurosurgery

The budget impact of publicly funding MRgFUS neurosurgery depends on how it is implemented. We assumed that MRgFUS neurosurgery may be implemented in several possible scenarios (Table 39). In the reference case, we assumed that the Ministry of Health and Long-Term Care would fund MRgFUS neurosurgery at the current level of 48 cases per year and, for simplicity, that MRgFUS neurosurgery would not replace other surgical procedures. In scenario analyses, we assumed that the Ministry of Health and Long-Term Care would fund a certain number of MRgFUS neurosurgery procedures each year, ranging from 60 to 144 cases. This increase in cases results from the fact that MRgFUS neurosurgery is a noninvasive procedure, and we therefore expected that demand for this procedure would be high were it to be publicly funded. With greater public awareness of MRgFUS neurosurgery, neurologists may refer more patients for the procedure. In the last scenario, we assumed that MRgFUS neurosurgery would replace both deep brain stimulation and radiofrequency thalamotomy once it is publicly funded. We did not include Gamma Knife thalamotomy since we did not include it as a comparator in the primary economic evaluation.

Table 39: Number of Neurosurgical Procedures Performed in the Current and New Scenarios

Scenario	Number of Publicly Funded MRgFUS Neurosurgery Procedures per Year	Treatment Replaced by MRgFUS Neurosurgery (n)
Current Scenario		
Reference Case	0	–
New Scenario		
Reference Case	48	No surgery
Scenario 1	60	No surgery
Scenario 2	72	No surgery
Scenario 3	96	No surgery
Scenario 4	144	No surgery
Scenario 5	62	No surgery (52.2) Deep brain stimulation (8.4) Radiofrequency thalamotomy (1.4)

Abbreviation: MRgFUS, magnetic resonance-guided focused ultrasound.

Resources and Costs

We included both treatment- and disease-related costs in the budget impact analysis. We obtained the relevant costs by running the cost-utility analysis over 5 years without discounting. Table 40 presents the annual per-patient costs in years 1 to 5 for each treatment strategy.

Table 40: Annual Per-Patient Cost for Each Treatment Strategy

Year	No Surgery, \$	MRgFUS Neurosurgery, \$	Radiofrequency Thalamotomy, \$	Deep Brain Stimulation, \$
Year 1	437	20,964	12,844	40,582
Year 2	427	731	599	1,868
Year 3	417	700	576	1,824
Year 4	406	668	554	1,777
Year 5	394	637	531	11,769

Abbreviation: MRgFUS, magnetic resonance-guided focused ultrasound.
 Note: All costs presented in 2017 Canadian dollars.

Analysis

We estimated the net budget impact of MRgFUS neurosurgery as the cost difference between two scenarios: the current scenario (no public funding) and the new scenario (with public funding). We conducted a reference case analysis and sensitivity analyses. Our reference case analysis represents the analysis with the most likely set of input parameters and model assumptions. In sensitivity analyses, we explored the variability in budget impact resulting from changing key input parameters and model assumptions (see Table 39).

Results

Table 41 presents the results of the reference case analysis. In the current scenario, in which MRgFUS neurosurgery is not publicly funded, the total cost per year ranges from \$20,957 in year 1 to \$99,941 in year 5 for people receiving no surgery. In the new scenario, in which MRgFUS neurosurgery is publicly funded, the total cost per year ranges from \$1,006,266 in year 1 to \$1,137,586 in year 5 for people receiving MRgFUS neurosurgery. Table 42 presents the resulting 5-year net budget impact. When considering the cost of the primary surgery only, the net budget impact is \$949,739 per year (i.e., the cost of funding 48 MRgFUS neurosurgery procedures per year), for a total of \$4,748,697 over 5 years.

Table 43 presents the results of the scenario analyses. In scenarios 1 to 4, in which we assumed MRgFUS neurosurgery would only replace no surgery, the net budget impact increased proportionally as the number of MRgFUS procedures funded increased. In scenario 5, in which we assumed MRgFUS neurosurgery would replace no surgery, deep brain stimulation, and radiofrequency thalamotomy, the net budget impact was reduced to \$831,882 in year 1 and \$763,063 in year 5.

Table 41: Reference Case Analysis Results

	Year 1	Year 2	Year 3	Year 4	Year 5	5-Year Total
Current Scenario: No Surgery^a						
Total cost, \$	20,957	41,466	61,492	80,997	99,941	304,852
Cost of primary surgery only, \$	—	—	—	—	—	—
New Scenario: MRgFUS Neurosurgery^a						
Total cost, \$	1,006,266	1,041,364	1,074,947	1,107,021	1,137,586	5,367,185
Cost of primary surgery only, \$	949,739	949,739	949,739	949,739	949,739	4,748,697
Net Budget Impact^a						
Total cost, \$	985,309	999,898	1,013,456	1,026,025	1,037,645	5,062,332
Cost of primary surgery only, \$	949,739	949,739	949,739	949,739	949,739	4,748,697

Abbreviation: MRgFUS, magnetic resonance-guided focused ultrasound.

Note: All costs presented in 2017 Canadian dollars.

^a48 patients per year.

Table 42: Five-Year Net Budget Impact of Publicly Funding MRgFUS

Year	Net Budget Impact, \$
Year 1	985,309
Year 2	999,898
Year 3	1,013,456
Year 4	1,026,025
Year 5	1,037,645
Total	5,062,332

Abbreviation: MRgFUS, magnetic resonance-guided focused ultrasound.

Budget Impact Analysis

January 2018

Table 43: Scenario Analysis Results—Net Budget Impact

	Year 1	Year 2	Year 3	Year 4	Year 5	5-Year Total
Scenario 1: 60 patients per year (MRgFUS neurosurgery replacing no surgery)						
Total cost, \$	1,231,637	1,249,872	1,266,819	1,282,531	1,297,057	6,327,915
Cost of primary surgery only, \$	1,187,174	1,187,174	1,187,174	1,187,174	1,187,174	5,935,871
Scenario 2: 72 patients per year (MRgFUS neurosurgery replacing no surgery)						
Total cost, \$	1,477,964	1,499,846	1,520,183	1,539,037	1,556,468	7,593,498
Cost of primary surgery only, \$	1,424,609	1,424,609	1,424,609	1,424,609	1,424,609	7,123,045
Scenario 3: 96 patients per year (MRgFUS neurosurgery replacing no surgery)						
Total cost, \$	1,970,618	1,999,795	2,026,911	2,052,049	2,075,290	10,124,665
Cost of primary surgery only, \$	1,899,479	1,899,479	1,899,479	1,899,479	1,899,479	9,497,394
Scenario 4: 144 patients per year (MRgFUS neurosurgery replacing no surgery)						
Total cost, \$	2,955,928	2,999,693	3,040,367	3,078,074	3,112,936	15,186,997
Cost of primary surgery only, \$	2,849,218	2,849,218	2,849,218	2,849,218	2,849,218	14,246,091
Scenario 5: 62 patients per year (MRgFUS neurosurgery replacing no surgery, DBS, and RF)						
Total cost, \$	831,882	837,104	841,387	844,805	763,063	4,118,240
Cost of primary surgery only, \$	813,194	813,194	813,194	813,194	813,194	4,065,971

Abbreviations: DBS, deep brain stimulation; MRgFUS, magnetic resonance-guided focused ultrasound; RF, radiofrequency.

Note: All costs presented in 2017 Canadian dollars.

Discussion

Our analysis shows that publicly funding MRgFUS neurosurgery at the current level of 48 cases per year would lead to a total 5-year budget impact of \$5 million, about \$1 million each year. If considering only the cost of the primary surgery, the budget impact would be \$0.95 million each year.

Our budget impact analysis has several strengths. We estimated both the potential demand (number of patients potentially eligible for surgery) and supply (current volume of surgeries performed) for essential tremor neurosurgeries. We estimated the number of patients potentially eligible for surgery based on published epidemiological data and clinical expert opinion, and we also obtained the actual volume of neurosurgeries performed in Ontario from local administrative databases. These data suggest that, as with other surgeries, there may be a gap between supply and demand for essential tremor neurosurgeries. Further, although deep brain stimulation and radiofrequency thalamotomy are currently publicly funded, very few people actually undergo either surgery. This may indicate an unmet need for noninvasive surgical procedures for the treatment essential tremor.

A limitation of our budget impact analysis is that we estimated the peri-procedural costs of deep brain stimulation and radiofrequency thalamotomy using the Ontario Case Costing database. This database has data from only a few facilities in the province; thus, the costs may not be representative of all facilities performing these procedures in Ontario.

Conclusions

We estimate the budget impact of publicly funding MRgFUS neurosurgery for the treatment of moderate to severe, medication-refractory essential tremor at the current level to be about \$1 million each year over the next 5 years.

PATIENT PREFERENCES AND VALUES

Objective

The objective of this analysis was to explore the underlying values, needs, impacts, and preferences of those with lived experience of essential tremor. The treatment focus was magnetic resonance-guided focused ultrasound (MRgFUS) neurosurgery versus standard care.

Background

Public and patient engagement explores the lived experience of a person with a health condition. It includes the impact that the condition and its treatment have on the patient and the patient's family and other caregivers, and on the patient's personal environment. Public and patient engagement increases awareness and builds appreciation for the needs, priorities, and preferences of people at the centre of a treatment program.

Lived experience is a unique source of evidence about the personal impact of a health condition and how that condition is managed. It includes what it is like to navigate the health care system and how technologies may or may not make a difference in people's lives. Information shared from lived experience can also identify gaps or limitations in published research (e.g., sometimes typical outcome measures do not reflect what is important to those with lived experience).¹¹³⁻¹¹⁵ Additionally, lived experience can provide information and perspectives on the ethical and social values implications of technologies and treatments.

Because the needs, priorities, preferences, and values of those with lived experience in Ontario are not often adequately explored in the published literature, we contact and speak directly with people who live with a given health condition, including those who may have experience with the intervention we are exploring.

Essential tremor has a substantial impact on the quality of life of people with the condition and their families. To better understand its impact on quality of life, we spoke with people with essential tremor and their families.

Several people we heard from had received treatment for their essential tremor through MRgFUS neurosurgery. Understanding and appreciating the day-to-day experience of living with essential tremor helps us contextualize the potential value of this treatment from the perspective of those with lived experience.

Methods

Engagement Plan

Engagement as a concept captures a range of efforts used to involve the public and patients in various domains and stages of decision-making for a health technology assessment.¹¹⁶ Rowe and Frewer outline three types of engagement: communication, consultation, and participation.¹¹⁷ Communication constitutes a one-way transfer of information from the sponsor to the individual, whereas participation involves the sponsor and individual collaborating through real-time dialogue. Consultation, however, refers to the sponsor seeking out information about the experience of the public, patients, and caregivers affected by the technology or intervention in question.¹¹⁸

The engagement plan for this health technology assessment focused on consultation. Within this typology, our design focused on interviews to elicit the lived experience of people with essential tremor and their families, including their experiences with MRgFUS neurosurgery.

We selected a qualitative interview as an appropriate methodology because this approach allows us to explore the central themes in participants' lived experience. Our main task in interviewing is to understand what participants tell us.¹¹⁹ Interviews are particularly useful for getting the story behind a participant's experiences, which was the objective of this portion of the health technology assessment. The sensitive nature of exploring quality of life for this topic is another factor supporting the use of interviews for this project.

Recruitment of Participants

We used an approach called purposive sampling¹²⁰⁻¹²² to actively recruit people with lived experience. We contacted people with essential tremor and their families through a variety of patient support organizations, health clinics, and foundations.

Inclusion Criteria

We sought to speak with people with essential tremor and their families. People with essential tremor were not required to have had direct experience with MRgFUS neurosurgery.

We sought broad geographic, cultural, and socioeconomic representations to elicit possible equity issues in accessing various treatment options for essential tremor.

Exclusion Criteria

We did not set specific exclusion criteria.

Participants

We conducted interviews with 14 people, including people with essential tremor and family members. While a small number of people with essential tremor had direct experience with MRgFUS neurosurgery, all participants were familiar with the treatment option and were able to speak to the values and preferences that would inform their decision-making with regard to pursuing this treatment option. Most of our participants live in the Greater Toronto Area, and a few live outside this area.

Interview Approach

At the beginning of the interview, we explained the mandate of Health Quality Ontario, the role of the Ontario Health Technology Advisory Committee, and the purpose of this health technology assessment. We outlined the risks of participation, and, through a letter of information, we explained how participants' personal health information would be protected (Appendix 9). We obtained verbal consent from participants before starting each interview (Appendix 10). We recorded and transcribed the interviews.

The interview consisted of a series of open-ended questions and lasted 20 to 40 minutes. We based our questions on a list of questions developed by Health Technology Assessment International's Interest Group on Patient and Citizen Involvement in HTA to elicit lived experiences specific to the impact of a health technology or intervention.¹²

Interview questions focused on the impact of essential tremor on the quality of life of those living with the condition and their families, experiences with treatment options for essential tremor, and the perceived benefits and people's expectations of MRgFUS neurosurgery. Appendix 11 provides our interview guide.

Data Extraction and Analysis

To capture themes and compare elements of lived experience among participants, we selected a modified version of a grounded theory methodology to analyze interview transcripts. The inductive nature of grounded theory follows an iterative process of eliciting, documenting, and analyzing responses while simultaneously collecting and analyzing data using a constant comparative approach.^{13,14} We coded transcripts and compared themes using NVivo (QSR International, Doncaster, Victoria, Australia). This qualitative software program helped us identify and interpret meaningful patterns in the interview data.

Results

Lived Experience of Essential Tremor

People with essential tremor with whom we spoke were diagnosed at various ages, from the teen years into people's 50s and 60s. These participants described a range of disease severity with a corresponding impact on quality of life. The degree to which people with essential tremor and their families made adjustments to their activities of daily living increased with the progression of the disease and the spread of the tremor. Typically, people with the condition reported first noticing tremor in their dominant hand. In a number of people with whom we spoke, the tremor then progressed to their other hand, head, lips, or feet.

All participants with the condition had been living with their tremor for a number of years and had developed various methods of compensating for the impact of the disease. One of the most common impacts mentioned was on people's ability to use their hands to perform tasks involving fine motor skills, such as eating and holding containers without spilling the contents:

"I'm able to function in the day-to-day environment. I'm able to function at home. I can cut grass. I do things at home. I bring my dinner plate over. I just use two hands. Right now, I had a cup of hot water. I don't fill it to the top. I fill it half-way up. This way, I know that I won't spill it."

"In the meantime, I can never be a waitress, and I can never be a brain surgeon, and I can't carry hot coffee or soup, and I can't carry much without spilling, but I've worked with it. So that's my story."

"It was okay for a while because, you know what? You learn. When you have an affliction like this all your life, you learn to compensate for it."

People with more severe tremor reported challenges with balance and an increased negative impact on their daily life. These people reported decreased participation in physical and social activities as a result of their tremor:

"I'm noticing I'm a little more...I'm all right most of the time, but sometimes when I move or something, I'm going somewhere and, like, even a familiar location like my home, all of a sudden, my balance just seems to get off for a second."

“We have a brand-new grandson...and I can’t feed him because my hands are shaking so much that I can’t make...I want to get the food in the mouth without it going on his face.”

In addition, several people who had developed essential tremor at a younger age found that it had affected their employment. Depending on the severity of the tremor, people reported that their employment options were restricted or that they had required modifications to perform their duties:

“I wanted to go into nursing at one point in time, and I was told absolutely not.”

“My hands are my living.”

“If I wasn’t careful in how I approached things or covered things up, I would probably have lost my job.”

Social situations were reported as particularly burdensome for those with essential tremor. People reported feeling embarrassed or frustrated in situations in which others would notice or ask about the tremor. A number of people reported feeling discriminated against, either in social situations or in the workplace:

“I remember what all people with tension tremor have to learn, which is either you better explain it clearly to everybody early, or you better hide it: one or the other. Because often they’ll assume the wrong thing, which is an unfortunate form of bigotry, but it’s reality, so you deal with it.”

“There was a problem with having to go use a computer and have coworkers make comments.”

“When you’re having a fine dining [experience] or an important executive meeting, other people would notice it. And they would...you could see the look in their eyes that [said] they would wonder, of course, ‘Has this guy got the heebie-jeebies from alcoholism?’ or just, ‘What happened?’”

People reported experiencing a variety of emotions related to their disease. Most commonly, people reported frustration and fear. Frustration was often a result of the consistent impact of tremor on people’s daily activities and a sense of loss of control. A number of people also spoke of worrying about and fearing disease progression and what the future might hold:

“Yeah, the frustration. Oh, I’ve picked stuff up, and I start throwing things around the kitchen.”

“Sometimes while I’m thinking about the fact my hands are shaking...well, it angers me a little, or I’m disappointed or something.”

“I guess I don’t like to look down the road.”

“It takes me longer than everybody else, but you know, you have to, you have to make the decision that this is what life is, and actually, the way I look at it is, if God wanted me to have a handicap, this is the one to have.”

Treatments for Essential Tremor

People with essential tremor typically reported taking medications to help control their tremor, although most felt these medications were only moderately effective. A number of people told us that they could not take medications for tremor owing to contraindications, and others reported unacceptable side effects. In addition, people told us that stressful or emotional situations could cause an exacerbation of tremor that could not be controlled by medication:

“[When I was] about 28 years old, the doctor put me on beta blockers, [but when] I was about 55, 60...I started to get side effects from beta blockers, and that's when I started looking into [MRgFUS].”

“But I didn't really feel that it [medication] did anything. I didn't bother taking [medication] anymore. So I haven't really...I've not had anything since about 2000.”

“Nowadays, it's even worse because [the doctor] is experimenting with different combinations to try to make the tremor stop, and it's getting a little worse actually.”

Some people reported self-medicating with alcohol to try to dull their tremor, and many of those who did not use alcohol in this way reported knowing or hearing of others who did:

“But if I had say, like, [with] three beers, it's fairly controllable. Like, it's still there, but...not too bad. I can sort of eat with a fork, that kind of thing. Usually if somebody invites me over for supper, I usually have two beers before I go or something like that, and they usually give me one there, and then I can sort of get through it, if you know what I mean.”

“The only good thing about it, that I saw online, that one of the possible [ways to] help is having a glass of vodka, and it does work. In other words, if we go out and I'm not driving, I'll have a vodka and tonic, and you know, that's two, two and a half hours I'm fine. I don't shake, no nothing.”

Disease progression and the lack of effective treatment with medication frustrated many people with essential tremor with whom we spoke and led them to seek out alternative treatments, such as surgery. To varying degrees, everyone we interviewed was familiar with surgical techniques to treat essential tremor, including MRgFUS neurosurgery. People often discussed weighing various factors, such as their degree of disability and their confidence in a particular procedure, when deciding whether to pursue a surgical treatment option. Most people expressed hesitation with regard to invasive surgical procedures, fearing the risks involved:

“I did go to one neurologist...about 10 years ago, and he suggested the surgery, deep brain stimulation...I don't think I would do that. I can sort of get by. I think that would be a little...kind of pushing it.”

“So I chose not to fool around with that. And with the surgery, I just didn't want to have holes dug in my head.”

"I'm afraid of that kind of surgery. I don't want anybody [going] into my head. I don't want the possible, even if it's a little possibility, [negative] consequence of it...I never liked pain, right?...I don't think I would ever have it."

MRgFUS Neurosurgery

Almost all people with essential tremor interviewed were familiar with the procedure of MRgFUS neurosurgery, even if they had not undergone the procedure. Recent media coverage of the procedure, along with information gained from social and patient groups, has raised the profile of this surgical option, and many people reported seeking out information about it. People reported speaking extensively with their health care providers about the procedure and conducting their own research online. The noninvasive aspect of the surgery is viewed positively compared with invasive surgical procedures:

"Surgically speaking, there was [deep brain stimulation], but [my tremor] was not serious enough at that time to warrant an operation like that. And then along comes MRgFUS, and, like I said, the rest was history. It had so many advantages, but the big one is, the huge one is the no cutting."

"I wanted to proceed ASAP [based] on the recommendation of my neurologist and also with some readings that I did."

For a number of people with essential tremor, making the decision to pursue surgery was difficult, despite receiving positive information about MRgFUS neurosurgery. Individual factors such as health, age, and the feelings of family members influenced people's decision-making, and some were uncertain whether they would ever undergo a surgical procedure. Given the length of wait times for surgical procedures, others expressed interest in being placed on the wait list and taking a wait-and-see approach:

"I thought if it got real bad, my daughters and my wife might say something to me, but I'm 86 and in fairly good health, and I move, and so I'm not so sure that I would consider something like that at that age unless it made me where I couldn't do anything."

"In 20 years, if I'm still around, I'm going to have a heck of a time [with] everything, I'm guessing, from eating, and I would never be able to drink tea from a cup. But so I thought, well, why wait until that point before I start thinking about what I can maybe do to alleviate some of the symptoms? And that's why I talked to [a neurologist] in the first place. And I thought I'd like to do it now and have the next 20 years not get any worse."

"You know, if the waiting list is a couple of years, then I can talk to my [doctor] and say, 'Put me on that list,' now."

People who had undergone MRgFUS neurosurgery reported a generally positive experience. People felt that they had been well prepared for what the procedure involved and were aware of the results they could expect. All of these people praised the professionalism and skill of their surgical teams:

"I knew what was going to come out the other end. There couldn't be anything but an improvement in this, [what] I'll call it my 6-inch tremor."

“And I met the guy who controls the machine for the intensity of the ultrasound. [He was a] very nice fellow, and he explained steps as we [went].”

Those who underwent MRgFUS neurosurgery did express frustration at the length of the wait time to receive the procedure. Many had lived with essential tremor for a number of years and were eager to resolve the issue:

“At the time, I felt some impatience because I had lived with it for so long, from 40 to 73 or so. So I had lived with it so long. And not knowing when death is going to come from some other reason, I was anxious to...I was very keen to progress forward in any way that I could help happen.”

“I think it could be very tough for people [who] have to wait two, three, four, five years for this. And I can only see the waiting lists increase and increase, because the team of people and the training they have to have to do everything so, so precisely.”

All people who had undergone the procedure reported positive results. Despite knowing what to expect, people still reported surprise at the immediate positive results. Being able to use their dominant hand again without tremor made it easier to perform daily tasks. Those who underwent the procedure considered themselves very lucky and reported being supportive of others undergoing this procedure:

“Having the treatment was, I thought, much of a miracle. Just having the ability to use one hand...that was a miraculous happening.”

“They pulled me out as normal, slid me out [of the MRI scanner] on the [sled]. And they said, “Okay, let’s do the scroll [the spiral-drawing task] first.” And, I kid you not, as soon as I did that, you could have heard me...more than a block away with the word ‘w-o-w.’ ‘Wow’...because it was such an improvement. It was everything at that moment.”

One person who had undergone MRgFUS neurosurgery reported experiencing tremor recurrence over time, but to a lesser degree than before the procedure. Others mentioned slight frustration that only one hand could be treated, not both. However, no other side effects were reported by those who had undergone the procedure:

“A million times better than it was, but it could still be better; there’s been a bit of a reverse.”

Discussion

Although only a small number of people with essential tremor have undergone MRgFUS neurosurgery in Ontario, we were able to speak with a number of these people, as well as others with essential tremor who have considered a variety of surgical treatments.

The majority of people with essential tremor with whom we spoke had mild to moderate symptoms, which they reported could have a large impact on their ability to perform daily tasks but did not require the use of additional supports or caregiver assistance. However, we did not interview any people with severe essential tremor who may require such supports or assistance.

All people with the condition whom we interviewed had lived with their tremor for a number of years and could speak to the progression of the disease, symptom management, different treatment options, and potential surgical options.

Those interviewed were supportive of MRgFUS neurosurgery and its positive treatment effect. However, despite this support, people acknowledged that, although it is a noninvasive procedure, it is still a surgical procedure, and the benefits may not outweigh the perceived risks. People reported considering many personal factors and other variables when deciding whether to pursue a surgical procedure, including MRgFUS neurosurgery.

People who had undergone MRgFUS neurosurgery spoke positively of their experience of both the procedure and the results they obtained. The most beneficial effect reported was a reduction or elimination of tremor in the dominant hand, which people reported as having a substantial beneficial effect on their ability to perform daily tasks and on their quality of life. However, some frustration was expressed at the long wait times for the procedure and the treatment effect being limited to the dominant hand.

Conclusions

People with essential tremor reported positive experiences with the procedure and results experienced with MRgFUS neurosurgery. The reduction or elimination of tremor in the dominant hand increased people's ability to perform daily tasks and improved their quality of life.

CONCLUSIONS OF THE HEALTH TECHNOLOGY ASSESSMENT

MRgFUS neurosurgery is an effective treatment for moderate to severe, medication-refractory essential tremor and has an acceptable safety profile. Important findings are as follows:

- In noncomparative studies, MRgFUS neurosurgery has been found to significantly improve tremor severity and quality of life and to significantly reduce functional disability in daily activities (low certainty in the evidence); MRgFUS neurosurgery has been found to be significantly more effective than a sham procedure (high certainty in the evidence)
- There are no significant differences in tremor severity or quality-of-life improvement or in functional disability reduction conferred by MRgFUS neurosurgery compared with deep brain stimulation (very low certainty in the evidence)
- There is no significant difference in tremor severity improvement conferred by MRgFUS neurosurgery compared with radiofrequency thalamotomy (very low certainty in the evidence)
- MRgFUS neurosurgery is associated with few complications and adverse effects, the vast majority of which are transient and resolve either entirely or to a point at which there is minimal interference with people's lives

Important findings of our economic analysis are as follows:

- As a noninvasive surgical procedure, MRgFUS neurosurgery is a good treatment option for people unable to undergo surgery owing to comorbidities and is also one of several reasonable surgical options
- In the subset of people with moderate to severe, medication-refractory essential tremor ineligible for invasive neurosurgery, the ICER of MRgFUS neurosurgery compared with no surgery is \$43,075 per QALY gained
- The province would need to spend about \$1 million a year over the next 5 years to publicly fund MRgFUS neurosurgery for the treatment of moderate to severe, medication-refractory essential tremor at the current level of 48 cases per year

Our engagement with people with lived experience of essential tremor found the following:

- As tremor severity increased, people reported a decrease in their ability to perform activities of daily living and in their quality of life
- Many reported being unable to take medication owing to contraindications or unacceptable side effects
- Most expressed hesitation regarding invasive neurosurgical procedures
- The noninvasive aspect of MRgFUS neurosurgery was viewed favourably
- People who had undergone MRgFUS neurosurgery reported positive experiences, both with the procedure itself and with the results

ABBREVIATIONS

CI	Confidence interval
CRST	Clinical Rating Scale for Tremors (a version of the Fahn–Tolosa–Marín Clinical Rating Scale for Tremor; <i>CRST</i> is used throughout to refer to both versions of the scale)
EQ-5D	European Quality of Life—5 Dimensions
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
FTM	Fahn–Tolosa–Marín Clinical Rating Scale for Tremor (note that <i>CRST</i> is used throughout to refer to both the <i>CRST</i> and <i>FTM</i> scales)
ICER	Incremental cost-effectiveness ratio
MRgFUS	Magnetic-resonance guided focused ultrasound
MRI	Magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
QALY	Quality-adjusted life years
QUEST	Quality of Life in Essential Tremor questionnaire
SD	Standard deviation

GLOSSARY

Blinded study	A study in which researchers, participants, or both are unaware of the treatment being administered.
Cost-effective	Good value for money; the overall benefit of the technique or intervention justifies the cost.
Cost–utility analysis	A type of analysis that estimates the value for money of an intervention by weighing the cost of the intervention against the improvements in length of life and quality of life. The result is expressed as a dollar amount per quality-adjusted life-year (QALY).
Deterministic sensitivity analysis	A type of analysis that changes the variables to determine whether the final answer will change. The analysis is done by first setting values for each factor, and then substituting other possible values for one (in a one-way sensitivity analysis) or more (in a multi-way sensitivity analysis) factors to test how these changes affect the result.
Discounting	A method that considers that costs and health benefits are worth more today than in the future.
Health state utility	The strength of patient preferences for a given state of health using a scale on which 1 represents full health and 0 represents dead. (Negative scores, meaning worse than dead, are possible.) Health state utility is an important data input in cost–utility models, but is also among the most uncertain inputs.
Incremental cost	The extra cost associated with using one test or treatment instead of another.
Incremental cost-effectiveness ratio (ICER)	Determines a unit of benefit for an intervention by dividing the incremental cost by the effectiveness. The incremental cost is the difference between the cost of the treatment under study and an alternative treatment. The effectiveness is usually measured as additional years of life or as quality-adjusted life years (QALYs).
Markov model	A type of modelling that measures the health state of a patient over the course of treatment. A patient may stay in one health state or move from one health state to another, depending on the effect of the treatment and the progression of the disease.
Monte Carlo simulation	Determines the uncertainty in an economic model by running many trials of the model. In each trial, random numbers are assigned wherever values are uncertain to see how the model result changes.
Open-label study	A study in which both researchers and participants are aware of the treatment being administered.
Probabilistic sensitivity analysis (PSA)	A type of analysis where the value of one or more unknown factors is estimated through the use of a technique that determines the most likely value or range of values for that factor. For instance, the Monte Carlo simulation will run a scenario many times using randomly assigned numbers where the value of a particular factor is unknown. The simulation indicates which outcomes are most common, and therefore most probable.

Quality-adjusted life-year (QALY)	A measurement that takes into account both the number of years gained by a patient from a procedure and the quality of those extra years (e.g., ability to function, freedom from pain). The QALY is commonly used as an outcome measure in cost–utility analyses.
Randomized controlled trial	A type of study in which subjects are assigned randomly into different groups, with one group receiving the treatment under study and the other group(s) receiving a different treatment or a placebo (no treatment) in order to determine the effectiveness of one approach compared with the other(s).
Reference case	A population or value used as a basis of comparison for the population under study. Where the population under study is said to deviate from a standard, this is the standard it deviates from.
Sensitivity	The ability of a test to accurately identify persons with the condition tested for (how well it returns positive results in persons who have the condition).
Sensitivity analysis	Every evaluation contains some degree of uncertainty. Study results can vary depending on the values taken by key parameters. Sensitivity analysis is a method that allows estimates for each parameter to be varied to show the impact on study results. There are various types of sensitivity analyses. Examples include deterministic, probabilistic, and scenario.
Statistical significance	The outcome of an analysis is statistically significant if the assumption that there is no effect (the null hypothesis) is sufficiently unlikely to be true. Typically, the outcome is considered statistically significant if there is less than a 5% chance that the outcome would have occurred if the null hypothesis were true.
Systematic review	A process to answer a research question by methodically identifying and assessing all available studies that evaluate the specified research question. The systematic review process is designed to be transparent and objective and is aimed at reducing bias in determining the answers to research questions.
Time horizon	Costs and outcomes are examined within a chosen time frame. In an economic evaluation, this time frame is referred to as the time horizon.

APPENDICES

Appendix 1: Literature Search Strategies

Clinical Evidence Search

Search date: April 11, 2017

Databases searched: All Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, CRD Health Technology Assessment Database, Cochrane Central Register of Controlled Trials, and NHS Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <March 2017>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to April 4, 2017>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2017 Week 15>, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy

-
- 1 Essential Tremor/ (6490)
 - 2 ((essential or familial or hereditary or heredofamilial or heredo-familial or juvenile or presenile or senile or benign or idiopathic) adj2 tremor*).ti,ab,kf. (8213)
 - 3 or/1-2 (9340)
 - 4 exp Thalamus/su [Surgery] (2626)
 - 5 ((thalam* and (surg* or neurosurg* or ablat*)) or thalamotom*).ti,ab,kf. (9462)
 - 6 Magnetic Resonance Imaging/ (693063)
 - 7 Magnetic Resonance Imaging, Interventional/ (3110)
 - 8 Ultrasonography, Interventional/ (20453)
 - 9 Ultrasonic Therapy/ (17555)
 - 10 High-Intensity Focused Ultrasound Ablation/ (3969)
 - 11 ((focus?ed ultrasound*1 or focus?ed ultrasonograph*) and (MRI or MR or MRI-guided or MR-guided or magnetic resonance* or unilateral or high-intensity)).ti,ab,kf. (7794)
 - 12 (MR?gFU* or MR?g-FU* or MR?gHIFU* or MR?-HIFU* or TcMR?gFU*).ti,ab,kf. (1270)
 - 13 (insightec* or exablate*).ti,ab,kf. (235)
 - 14 or/4-13 (747080)
 - 15 3 and 14 (1391)
 - 16 exp Animals/ not Humans/ (16078021)
 - 17 15 not 16 (1000)
 - 18 Case Reports/ or Comment.pt. or Editorial.pt. or Letter.pt. or Congresses.pt. (4852163)
 - 19 17 not 18 (880)
 - 20 limit 19 to english language [Limit not valid in CDSR; records were retained] (780)
 - 21 20 use ppez,coch,cctr,clhta,cleed (424)
 - 22 essential tremor/ (6490)
 - 23 ((essential or familial or hereditary or heredofamilial or heredo-familial or juvenile or presenile or senile or benign or idiopathic) adj2 tremor*).tw,kw. (8320)
 - 24 or/22-23 (9352)
 - 25 thalamotomy/ (1375)
 - 26 ((thalam* and (surg* or neurosurg* or ablat*)) or thalamotom*).tw,kw,dv. (9745)
 - 27 nuclear magnetic resonance imaging/ (652844)
 - 28 interventional magnetic resonance imaging/ (3110)

29 interventional ultrasonography/ (20453)
30 ultrasound therapy/ (8099)
31 high intensity focused ultrasound/ (5690)
32 ((focus?ed ultrasound*1 or focus?ed ultrasonograph*) and (MRI or MR or MRI-guided or MR-guided or magnetic resonance* or unilateral or high-intensity)).tw,kw,dv. (7933)
33 (MR?gFU* or MR?g-FU* or MR?gHIFU* or MR?-HIFU* or TcMR?gFU*).tw,kw,dv. (1329)
34 (insightec* or exablate*).tw,kw,dv. (354)
35 or/25-34 (697994)
36 24 and 35 (1588)
37 (exp animal/ or nonhuman/) not exp human/ (10171272)
38 36 not 37 (1573)
39 Case Report/ or Comment/ or Editorial/ or Letter/ or conference abstract.pt. (9188695)
40 38 not 39 (1029)
41 limit 40 to english language [Limit not valid in CDSR; records were retained] (927)
42 41 use emez (635)
43 21 or 42 (1059)
44 43 use ppez (401)
45 43 use emez (635)
46 43 use coch (0)
47 43 use cctr (21)
48 43 use clhta (2)
49 43 use cleed (0)
50 remove duplicates from 43 (721)

Grey Literature

Search date: April 12–13, 2017

Websites searched: HTA Database Canadian Repository, Alberta Health Technologies Decision Process reviews, Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), McGill University Health Centre Health Technology Assessment Unit, National Institute for Health and Care Excellence (NICE), Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Australian Government Medical Services Advisory Committee, Centers for Medicare & Medicaid Services Technology Assessments, Institute for Clinical and Economic Review, Ireland Health Information and Quality Authority Health Technology Assessments, Washington State Health Care Authority Health Technology Reviews, clinicaltrials.gov, Tufts Cost Effectiveness Analysis Registry

Keywords used: tremor, tremors, tremblement, thalamus, thalamotomy, ultrasound, ultrasounds, ultrasonography, ultrasonographies, ultrason, ultrasonographie, MRgFU, MRg-FU, MRgHIFU, MR-HIFU, TcMRgFU, MRlgFU, MRlg-FU, MRlgHIFU, MRI-HIFU, TcMRlgFU, MRgFUS, MRg-FUS, MRgHIFUS, MR-HIFUS, TcMRgFUS, MRlgFUS, MRlg-FUS, MRlgHIFUS, MRI-HIFUS, TcMRlgFUS, insightec, exablate

Results: 0

8 clinical trials not counted in PRISMA

Economic Literature Search

Search date: April 11, 2017

Databases searched: All Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, CRD Health Technology Assessment Database, Cochrane Central Register of Controlled Trials, and NHS Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <March 2017>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to April 4, 2017>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2017 Week 15>, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy

-
- 1 Essential Tremor/ (6490)
 - 2 ((essential or familial or hereditary or heredofamilial or heredo-familial or juvenile or presenile or senile or benign or idiopathic) adj2 tremor*).ti,ab,kf. (8213)
 - 3 or/1-2 (9340)
 - 4 exp Thalamus/su [Surgery] (2626)
 - 5 ((thalam* and (surg* or neurosurg* or ablat*)) or thalamotom*).ti,ab,kf. (9462)
 - 6 Magnetic Resonance Imaging/ (693063)
 - 7 Magnetic Resonance Imaging, Interventional/ (3110)
 - 8 Ultrasonography, Interventional/ (20453)
 - 9 Ultrasonic Therapy/ (17555)
 - 10 High-Intensity Focused Ultrasound Ablation/ (3969)
 - 11 ((focus?ed ultrasound*1 or focus?ed ultrasonograph*) and (MRI or MR or MRI-guided or MR-guided or magnetic resonance* or unilateral or high-intensity)).ti,ab,kf. (7794)
 - 12 (MR?gFU* or MR?g-FU* or MR?gHIFU* or MR?-HIFU* or TcMR?gFU*).ti,ab,kf. (1270)
 - 13 (insightec* or exablate*).ti,ab,kf. (235)
 - 14 or/4-13 (747080)
 - 15 3 and 14 (1391)
 - 16 economics/ (254251)
 - 17 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (794446)
 - 18 economics.fs. (397845)
 - 19 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (747961)
 - 20 exp "costs and cost analysis"/ (544587)
 - 21 (cost or costs or costing or costly).ti. (231064)
 - 22 cost effective*.ti,ab,kf. (265682)
 - 23 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab. (172651)
 - 24 models, economic/ (174032)
 - 25 markov chains/ or monte carlo method/ (70416)
 - 26 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (34175)
 - 27 (markov or markow or monte carlo).ti,ab,kf. (108821)
 - 28 quality-adjusted life years/ (33723)
 - 29 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (54963)

30 ((adjusted adj (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (88737)
 31 or/16-30 (2403893)
 32 15 and 31 (25)
 33 32 use ppez,coch,cctr,clhta (5)
 34 15 use cleed (0)
 35 33 or 34 (5)
 36 limit 35 to english language [Limit not valid in CDSR; records were retained] (5)
 37 essential tremor/ (6490)
 38 ((essential or familial or hereditary or heredofamilial or heredo-familial or juvenile or presenile or senile or benign or idiopathic) adj2 tremor*).tw,kw. (8320)
 39 or/37-38 (9352)
 40 thalamotomy/ (1375)
 41 ((thalam* and (surg* or neurosurg* or ablat*)) or thalamotom*).tw,kw,dv. (9745)
 42 nuclear magnetic resonance imaging/ (652844)
 43 interventional magnetic resonance imaging/ (3110)
 44 interventional ultrasonography/ (20453)
 45 ultrasound therapy/ (8099)
 46 high intensity focused ultrasound/ (5690)
 47 ((focus?ed ultrasound*1 or focus?ed ultrasonograph*) and (MRI or MR or MRI-guided or MR-guided or magnetic resonance* or unilateral or high-intensity)).tw,kw,dv. (7933)
 48 (MR?gFU* or MR?g-FU* or MR?gHIFU* or MR?-HIFU* or TcMR?gFU*).tw,kw,dv. (1329)
 49 (insightec* or exablate*).tw,kw,dv. (354)
 50 or/40-49 (697994)
 51 39 and 50 (1588)
 52 Economics/ (254251)
 53 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (130520)
 54 Economic Aspect/ or exp Economic Evaluation/ (435128)
 55 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw. (771955)
 56 exp "Cost"/ (544587)
 57 (cost or costs or costing or costly).ti. (231064)
 58 cost effective*.tw,kw. (276411)
 59 (cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab. (173723)
 60 Monte Carlo Method/ (57773)
 61 (decision adj1 (tree* or analy* or model*)).tw,kw. (37865)
 62 (markov or markow or monte carlo).tw,kw. (113775)
 63 Quality-Adjusted Life Years/ (33723)
 64 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw. (58721)
 65 ((adjusted adj (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw. (107774)
 66 or/52-65 (1912130)
 67 51 and 66 (34)
 68 67 use emez (29)
 69 limit 68 to english language [Limit not valid in CDSR; records were retained] (29)
 70 36 or 69 (34)
 71 70 use ppez (5)
 72 70 use emez (29)
 73 70 use coch (0)
 74 70 use cctr (0)
 75 70 use clhta (0)

- 76 70 use cleed (0)
- 77 remove duplicates from 70 (31)

Health State Utility Literature Search

Search date: April 11, 2017

Databases searched: All Ovid MEDLINE

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy

-
- 1 Essential Tremor/ (1597)
 - 2 ((essential or familial or hereditary or heredofamilial or heredo-familial or juvenile or presenile or senile or benign or idiopathic) adj2 tremor*).ti,ab,kf. (3287)
 - 3 or/1-2 (3466)
 - 4 Quality-Adjusted Life Years/ (9421)
 - 5 (quality adjusted or adjusted life year*).tw. (12135)
 - 6 (qaly* or qald* or qale* or qtime*).tw. (7843)
 - 7 (illness state\$1 or health state\$1).tw. (5246)
 - 8 (hui or hui1 or hui2 or hui3).tw. (1198)
 - 9 (multiattribute* or multi attribute*).tw. (709)
 - 10 (utility adj3 (score\$1 or valu* or health* or cost* or measure* or disease* or mean or gain or gains or index*)).tw. (11110)
 - 11 utilities.tw. (5641)
 - 12 (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eurqol5d or euro?qul or eur?qul5d or euro* quality of life or European qol).tw. (7574)
 - 13 (euro* adj3 (5 d or 5d or 5 dimension* or 5dimension* or 5 domain* or 5domain*)).tw. (2564)
 - 14 (sf36* or sf 36* or sf thirtysix or sf thirty six).tw. (18577)
 - 15 (time trade off\$1 or time tradeoff\$1 or tto or timetradeoff\$1).tw. (1606)
 - 16 ((qol or hrqol or quality of life).ti. or *quality of life/) and ((qol or hrqol* or quality of life) adj2 (increas* or decreas* or improve* or declin* or reduc* or high* or low* or effect or effects of worse or score or scores or change\$1 or impact\$1 or impacted or deteriorate\$)).ab. (24011)
 - 17 Cost-Benefit Analysis/ and (cost effectiveness ratio* and (perspective* or life expectanc*)).tw. (2537)
 - 18 *quality of life/ and (quality of life or qol).ti. (43776)
 - 19 quality of life/ and ((quality of life or qol) adj3 (improve* or chang*)).tw. (19022)
 - 20 quality of life/ and ((quality of life or qol) adj (score\$1 or measure\$1)).tw. (9452)
 - 21 quality of life/ and health-related quality of life.tw. (23854)
 - 22 quality of life/ and ec.fs. (8622)
 - 23 quality of life/ and (health adj3 status).tw. (7328)
 - 24 (quality of life or qol).tw. and cost-benefit analysis/ (9635)
 - 25 models, economic/ (8246)
 - 26 or/4-25 (126359)
 - 27 3 and 26 (33)
 - 28 limit 27 to english language (32)

Targeted Literature Search

Search date: July 11, 2017

Databases searched: All Ovid MEDLINE, Cochrane Database of Systematic Reviews

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to July 6, 2017>, All Ovid MEDLINE(R) <1946 to Present>

Search Strategy

-
- 1 Essential Tremor/ (1642)
 - 2 ((essential or familial or hereditary or heredofamilial or heredo-familial or juvenile or presenile or senile or benign or idiopathic) adj2 tremor*).ti,ab,kf. (3355)
 - 3 or/1-2 (3536)
 - 4 Deep Brain Stimulation/ (6611)
 - 5 (((brain or thalam* or subthalam*) adj3 (stimulat* or stimulus or stimuli)) or DBS).ti,ab,kf. (21617)
 - 6 Electric Stimulation Therapy/ (19160)
 - 7 Electric Stimulation/ (111699)
 - 8 ((electric* adj3 (stimulat* or stimulus or stimuli)) or electrotherap* or electro-therap* or electric therap* or electrostimulat* or electro-stimulat*).ti,ab,kf. (70115)
 - 9 Thalamus/su [Surgery] (1396)
 - 10 ((thalam* and (surg* or neurosurg* or ablat*)) or thalamotom*).ti,ab,kf. (4113)
 - 11 (radiofrequenc* or radio-frequenc*).ti,ab,kf. (36657)
 - 12 Stereotaxic Techniques/ (14729)
 - 13 (stereotactic or stereotaxic).ti,ab,kf. (25581)
 - 14 or/4-13 (242728)
 - 15 3 and 14 (932)
 - 16 Meta Analysis.pt. (82825)
 - 17 Meta-Analysis/ or Meta-Analysis as Topic/ or exp Technology Assessment, Biomedical/ (108105)
 - 18 (((systematic* or methodologic*) adj3 (review* or overview*)) or pooled analysis or published studies or published literature or hand search* or handsearch* or medline or pubmed or embase or cochrane or cinahl or data synthes* or data extraction* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).ti,ab. (260255)
 - 19 (meta analy* or metaanaly* or health technolog* assess*).mp. (157987)
 - 20 or/16-19 (333350)
 - 21 15 and 20 (29)
 - 22 21 use ppez (29)
 - 23 15 use coch (0)
 - 24 22 or 23 (29)
 - 25 limit 24 to english language [Limit not valid in CDSR; records were retained] (26)

Grey Literature

Search date: April 12–13, 2017

Websites searched: HTA Database Canadian Repository, Alberta Health Technologies Decision Process reviews, Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), McGill University Health Centre Health Technology Assessment Unit, National Institute for Health and Care Excellence (NICE), Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Australian Government Medical Services Advisory Committee, Centers for Medicare & Medicaid Services Technology Assessments, Institute for Clinical and Economic Review, Ireland Health Information and Quality Authority Health Technology Assessments, Washington State Health Care Authority Health Technology Reviews, clinicaltrials.gov, Tufts Cost Effectiveness Analysis Registry

Keywords used: tremor, tremors, tremblement, thalamus, thalamotomy, ultrasound, ultrasounds, ultrasonography, ultrasonographies, ultrason, ultrasonographie, MRgFU, MRg-FU, MRgHIFU, MR-HIFU, TcMRgFU, MRlgFU, MRlg-FU, MRlgHIFU, MRI-HIFU, TcMRlgFU, MRgFUS, MRg-FUS, MRgHIFUS, MR-HIFUS, TcMRgFUS, MRlgFUS, MRlg-FUS, MRlgHIFUS, MRI-HIFUS, TcMRlgFUS, insightec, exablate

Results: 0

Trial registry results not reported in PRISMA: 8

Appendices

Appendix 2: Risk-of-Bias Assessment

Table A1: Risk of Bias^a Among Randomized Controlled Trials

Author, Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Incomplete Outcome Data	Selective Reporting	Other Bias
Elias et al, 2016 ³⁸	Low	Low	Low	Low	Low	Low ^b

^aPossible risk of bias judgments: low, high, and unclear, based on the Cochrane Risk of Bias tool for randomized controlled trials.³³

^bThis study was supported by funds from InSightec, the Focused Ultrasound Foundation, and the Binational Industrial Research and Development Foundation, and some authors disclosed receipt of funding from InSightec. However, the statistical analysis was planned and conducted with the assistance of an outside biostatistics team according to the protocol approved by the U.S. Food and Drug Administration.

Table A2: Risk of Bias^a Among Nonrandomized Studies

Author, Year	Selection of Participants	Confounding Variables	Measurement of Exposure	Blinding of Outcome Assessments	Incomplete Outcome Data	Selective Outcome Reporting
Kim et al, 2017 ⁴⁶	Low	Low	Low	Unclear	Low	Low
Shreglmann et al, 2017 ⁴²	Unclear	Low	Low	Low	Low	Low
Zaaroor et al, 2017 ⁴⁵	Unclear	Low	Low	Unclear	Unclear	Low
Gallay et al, 2016 ³⁹	Low	Low	Low	Unclear	High	Unclear
Chang et al, 2015 ^{36,b}	Unclear	Low	Low	Unclear	Low	Low
Huss et al, 2015 ⁴⁰	High	Unclear	Low	Unclear	Low	Low
Elias et al, 2013 ^{37,c}	Unclear	Low	Low	Low	Low	Low
Lipsman et al, 2013 ^{41,d}	Unclear	Low	Low	High	Low	Low

^aPossible risk of bias judgments: low, high, and unclear, based on the Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS).

^bThis study was supported by an InSightec research grant, and InSightec provided technical assistance for the procedures during the study.

^cThis study was supported by funding from the Focused Ultrasound Surgery Foundation. InSightec provided technical assistance during procedures and financial contributions to the Focused Ultrasound Surgery Foundation, and their representatives were responsible for regulatory compliance throughout study. The University of Virginia collected and analyzed all data, and the authors vouch for accuracy and fidelity to protocol.

^dThis study was supported by funding from the Focused Ultrasound Foundation. InSightec assisted with technical aspects of procedures and was responsible for regulatory compliance throughout study. The sponsor had no role in study design, data collection, analysis, interpretation, or writing the article, and the corresponding author had full access to the data and final decision on submission for publication.

Appendix 3: Selected Excluded Studies—Clinical Evidence Review

Table A3 provides a selection of studies that readers may have expected to see in the clinical evidence review of this health technology assessment. These studies were screened but did not meet the inclusion criteria.

Table A3: Selected Excluded Studies

Citation	Primary Reason for Exclusion
Bauer R, Martin E, Haegele-Link S, Kaegi G, von Specht M, Werner B. Noninvasive functional neurosurgery using transcranial MR imaging-guided focused ultrasound. <i>Parkinsonism Relat Disord.</i> 2014;20 Suppl 1:S197-9.	Study type (narrative review)
Dallapiazza R, McKisic MS, Shah B, Elias WJ. Neuromodulation for movement disorders. <i>Neurosurg Clin N Am.</i> 2014;25(1):47-58.	Intervention (deep brain stimulation)
Hariz M. Focused ultrasound thalamotomy improves essential tremor. <i>Mov Disord.</i> 2013;28(13):1803.	Study type (commentary)
Jeanmonod D, Werner B, Morel A, Michels L, Zadicario E, Schiff G, et al. Transcranial magnetic resonance imaging-guided focused ultrasound: noninvasive central lateral thalamotomy for chronic neuropathic pain. <i>Neurosurg Focus.</i> 2012;32(1):E1.	Population (neuropathic pain)
Jolesz FA, McDannold NJ. Magnetic resonance-guided focused ultrasound: a new technology for clinical neurosciences. <i>Neurol Clin.</i> 2014;32(1):253-69.	Study type (narrative review)
Jung HH, Chang WS, Rachmilevitch I, Tlusty T, Zadicario E, Chang JW. Different magnetic resonance imaging patterns after transcranial magnetic resonance-guided focused ultrasound of the ventral intermediate nucleus of the thalamus and anterior limb of the internal capsule in patients with essential tremor or obsessive-compulsive disorder. <i>J Neurosurg.</i> 2015;122(1):162-8.	Outcome (MRI patterns)
Martin E, Werner B. Focused ultrasound surgery of the brain. <i>Curr Radiol Rep.</i> 2013;1(2):126-35.	Study type (narrative review)
Monteith S, Sheehan J, Medel R, Wintermark M, Eames M, Snell J, et al. Potential intracranial applications of magnetic resonance-guided focused ultrasound surgery. <i>J Neurosurg.</i> 2013;118(2):215-21.	Study type (narrative review)
Moser D, Zadicario E, Schiff G, Jeanmonod D. MR-guided focused ultrasound technique in functional neurosurgery: targeting accuracy. <i>J Ther Ultrasound.</i> 2013;1:3.	Outcome (targeting accuracy)
Ravikumar VK, Parker JJ, Hornbeck TS, Santini VE, Pauly KB, Wintermark M, et al. Cost-effectiveness of focused ultrasound, radiosurgery, and DBS for essential tremor. <i>Mov Disord.</i> 2017.	Study type (economic analysis)

Abbreviations: DBS, deep brain stimulation; MRI, magnetic resonance imaging.

Appendix 4: Applicability and Methodological Quality of the Included Economic Study

Table A4: Applicability of the Included Economic Study—Ravikumar et al, 2017⁵⁴

Question	Response
Is the study population similar to the question?	Partially. The study evaluated people with medication-resistant essential tremor eligible for surgical treatment, but did not consider people unsuitable for surgical treatment.
Are the interventions similar to the question?	Partially. The study excluded radiofrequency thalamotomy in the main analysis; the estimated cost was included only in the appendix.
Is the health care system in which the study was conducted sufficiently similar to the current Ontario context?	No. U.S. societal perspective.
Was/were the perspective(s) clearly stated, and what were they?	Yes. U.S. societal perspective.
Are estimates of relative treatment effect from the best available sources?	Uncertain, since nearly all included reports are uncontrolled observational studies, and a detailed assessment of the quality of each study is not available.
Are all future costs and outcomes discounted? (If yes, at what rate?)	Unclear, as the publication did not report the model time horizon.
Is the value of health effects expressed in terms of quality-adjusted life-years?	Yes, although how utility was derived was not clearly reported.
Are costs and outcomes from other sectors fully and appropriately measured and valued?	No. The study appears to include only direct medical costs, although the authors stated they were using a societal perspective.
Overall judgment	Partially applicable

Table A5: Methodological Quality of Included Economic Study (Ravikumar et al 2017⁵⁴)

Question	Possible responses
Does the model structure adequately reflect the nature of the health condition under evaluation?	No. It did not include long-term clinical outcomes such as tremor recurrence.
Is the time horizon sufficiently long to reflect all important differences in costs and outcomes? (e.g., if the rate of mortality differs between interventions, does the model take a lifetime horizon?)	No. The time horizon used is unclear; it appears to be short-term.
Are all important and relevant health outcomes included?	Partly. Improvement in functional disability was associated with a different treatment, which was not reported.
Are the estimates of relative treatment effects obtained from the best available sources?	Partly. Nearly all included reports are uncontrolled observational studies.
Do the estimates of relative treatment effect match the estimates contained in the clinical report?	Not applicable. We were unable to check since the estimates were not reported clearly.
Are all important and relevant (direct) costs included in the analysis?	No. The publication did not include long-term costs such as treatment for tremor recurrence and deep brain stimulation device battery replacement.
Are the estimates of resource use obtained from the best available sources?	Yes.
Are the unit costs of resources obtained from the best available resources?	Yes.
Is an appropriate incremental analysis presented, or can it be calculated from the reported data?	Yes.
Are all important and uncertain parameters subjected to appropriate sensitivity analysis?	Unclear. The sensitivity analysis results were not fully presented.
Is there a potential conflict of interest?	Unclear.
Overall assessment	Minor limitations

Appendix 5: Health State Utility Search Results

Table A3 summarizes the results of our health state utility search.

We found one study that measured the health state utility of people with essential tremor before and after pharmacological treatment. Herceg et al⁸³ included 29 people with essential tremor severe enough to produce disability. Nine of the 29 people had previously received propranolol or primidone as monotherapy or in combination without satisfactory outcome. In the study, people were treated with pramipexole for 16 weeks and evaluated every 4 weeks. At baseline, people had a mean score of 18.50 points on part A of the FTM scale (FTM-A) and a mean score of 0.69 on the EQ-5D. At 4 months, the FTM-A score had improved by 65% (6.60 points), and the EQ-5D score had increased to 0.91. We decided to use utility values from this study because the patient population was similar to our model population (as defined by having similar FTM-A and FTM total scores at baseline and after treatment).

One Spanish study measured the health state utility of people with essential tremor.⁵⁵ The majority of people had mild to moderate tremor (42.4% and 43.2%, respectively); 13.6% had severe tremor. Also, most people had received no medication (32.2%) or just one medication (47.46%) for essential tremor. The mean EQ-5D score was 0.73 (SD: 0.30), and the mean QUEST summary index was 19.91. We did not use the value from this study because the patient population had less severe disease compared with our model population.

Three studies measured the health state utility of people with definite or probable essential tremor compared with healthy controls using the 36-Item Short-Form Survey (SF-36).¹⁰⁷⁻¹⁰⁹ We used a mapping algorithm from a study by Ara et al¹²³ to convert the eight mean SF-36 dimension scores reported by these studies into a mean EQ-5D utility score. The utility value of people living with essential tremor was found to be between 0.7 and 0.8, compared with the utility value of healthy controls, which ranged from 0.84 to 0.90. We did not use the health state utility values from these studies since the patient population was not representative of our model population.

We also identified two studies reporting on quality-of-life improvement after deep brain stimulation, measured using a visual analog scale.^{26,67} In 2002, Hariz et al⁶⁷ found that quality of life improved by 31.3 point between 6 and 26 months following the procedure. In 2008, Hariz et al²⁶ found that quality of life improved by 34 points at 1 year, and by 18 points at 7 years. We did not use these data for the estimation of health state utility increments after MRgFUS neurosurgery as they were derived from a visual analog scale.

Last, we did not consider health state utility values of people with tremor resulting from other types of movement disorder (e.g., dystonia, multiple sclerosis, Parkinson's disease) as an approximation for those of people with essential tremor. This is because people with other types of movement disorder experience non-tremor-related symptoms and disabilities in addition to tremor, whereas tremor is the main symptom in essential tremor.

Table A6: Summary of Results: Health State Utility Search

Author, Year	Patient Population	Health State	Results
EQ-5D			
Martinez-Martin et al, 2010 ⁵⁵	Essential tremor, mild to moderate	Essential tremor, treatment unspecified	ET = 0.73
Herceg et al, 2012 ⁸³	Essential tremor, tremor severe enough to produce disability	Before and after drug treatment (pramipexole)	Baseline = 0.69 (FTM-A = 18.5; FTM total = 43.71) 4 months = 0.91 (FTM-A = 6.60; FTM total = 20.75)
VAS			
Hariz et al, 2002 ⁶⁷	Essential tremor, medication refractory	Before and after deep brain stimulation, 6–26 months	VAS improved by 31.3 points
Hariz et al, 2008 ²⁶	Essential tremor, medication refractory	Before and after deep brain stimulation, 1 year, 7 years	VAS improved by 34 points at 1 year and by 18 points at 7 years
SF-36			
Lorenz et al, 2006 ¹⁰⁷	Essential tremor, definite or probable	Essential tremor, treatment unspecified	ET = 0.80; control = 0.90
Nguyen et al, 2007 ¹⁰⁸	Essential tremor, community-dwelling, newly diagnosed, aged ≥ 65 years	Essential tremor, treatment unspecified	ET = 0.70; control = 0.84
Musacchio et al, 2016 ¹⁰⁹	Essential tremor, definite or probable (FTM score at baseline = 36.8)	Essential tremor, treatment unspecified	ET = 0.76; control = 0.86

Abbreviations: EQ-5D, European Quality of Life—5 Dimensions; ET, essential tremor; FTM, Fahn–Tolosa–Marin Clinical Rating Scale for Tremor; SF-36, 36-Item Short-Form Survey; VAS, visual analog scale.

Appendix 6: Cost Inputs

Table A7: Cost Components of the Deep Brain Stimulation System

Item	Quantity	Unit Cost, \$ (2011 CAD)	Unit Cost, \$ (2017 CAD)
Activa SC (unilateral)			
Implanted pulse generator	1	7,995	8,375
Deep brain electrode lead	1	1,995	2,090
Extension lead	1	1,745	1,828
Patient activator	1	1,295	1,357
Total cost		13,030	13,649
Activa PC (bilateral)			
Implanted pulse generator	1	10,995	11,517
Deep brain electrode lead	2	1,995	2,090
Extension lead	2	1,745	1,828
Patient activator	1	1,295	1,357
Total cost		19,770	20,709

Source: Medtronic of Canada Ltd., 2011.¹²⁴

Table A8: Surgical Assistant Service Costs

	Procedure			Source
	MRgFUS	DBS	RF	
Average surgery length, hours	3.5	4.5	3	Expert opinion
Number of basic units	9	9	9	Schedule of Benefits (N124) ⁹¹
Number of time units	28	40	22	Calculated based on average surgery length
Total number of units	37	49	31	
Total billing	\$445	\$590	\$373	

Abbreviations: DBS, deep brain stimulation; MRgFUS, magnetic resonance-guided focused ultrasound; RF, radiofrequency.

Note: The amount payable for surgical assistant service is calculated by adding the number of basic and time units and multiplying the total by the surgical assistant unit fee (\$12.04/unit). For surgical assistant, there are 9 base units and 1 unit per 15 minutes in the first hour, 2 units per 15 minutes after the first hour, and 3 units per 15 minutes after 2.5 hours.

Table A9: Anaesthesia Service Costs

	Procedure			Source
	MRgFUS	DBS	Radiofrequency	
Average surgery length, hours	3.5	4.5	3	Expert opinion
Number of basic units	11	11	11	Schedule of Benefit (N124) ⁹¹
Number of time units	28	40	22	Calculated based on average surgery length
Total number of units	39	51	33	
Total billing	\$585	\$766	\$495	

Abbreviations: DBS, deep brain stimulation; MRgFUS, magnetic resonance-guided focused ultrasound; RF, radiofrequency.

Note: The amount payable for anaesthesia service is calculated by adding the number of basic and time units and multiplying the total by the anaesthesiologist unit fee (\$15.01/unit). For anaesthesia services, there are 11 base units and 1 unit per 15 minutes in the first hour, 2 units per 15 minutes after the first hour, and 3 units per 15 minutes after 2.5 hours.

Appendix 7: Probabilistic Analysis Model Variables and Distributions

Table A10: Probabilistic Analysis Model Variables and Distributions

Parameter	Distribution	Source			
Improvement post-surgery (MRgFUS, RF, DBS)		Mean	Alpha	Beta	
Proportion with marked improvement	Beta	53%	27	24	Elias et al, 2016 ³⁸
Proportion with mild to moderate improvement	Varies with the above	47%	–	–	
Probability of recurrence^a (MRgFUS, RF)					
Annual probability of recurrence after MRgFUS or RF thalamotomy in year 1	Beta	8.9%	5	51	Elias et al, 2016 ³⁸
Annual probability of recurrence after MRgFUS or RF thalamotomy in years 2–5	Varies with the above	4.7%	–	–	Calculated
Probability of reoperation (MRgFUS, RF)					
Probability of reoperation after recurrence	Beta	40%	2	3	Elias et al, 2016 ³⁸
Costs		Mean	SD	Sample Size	
DBS hospitalization cost	Gamma	\$17,221	\$3,043	10	OCC ⁹²
RF hospitalization cost	Gamma	\$6,822	\$5,140	9	OCC ⁹²
DBS monitoring cost, year 1	Gamma	\$1,249	\$468	36	Ondo et al, 2005 ⁹⁷
DBS monitoring cost, subsequent years	Gamma	\$463	\$261	36	Ondo et al, 2005 ⁹⁷
Utilities		Mean	SD	Sample Size	
Alive with disabling tremor (baseline)	Beta	0.69	0.30	24	Herceg et al, 2012 ⁸³
No recurrence, marked improvement	Beta	0.91	0.08	24	

Abbreviations: DBS, deep brain stimulation; MRgFUS, magnetic resonance-guided focused ultrasound; OCC, Ontario Case Costing database; RF, radiofrequency.

^aRecurrence refers to diminished tremor control to the point of requiring reoperation.

Appendix 8: Additional Results Tables

Research Question 1: What is the cost-effectiveness of MRgFUS neurosurgery compared with standard treatment (i.e., no surgery) for people with moderate to severe, medication-refractory essential tremor, who are ineligible for invasive neurosurgery, within the context of the Ontario Ministry of Health and Long-Term Care?

Table A11: Probabilistic Reference Case Analysis Results—MRgFUS Neurosurgery Versus No Surgery

	MRgFUS, Mean (95% CI)	No Surgery, Mean (95% CI)
Cost of primary surgery	\$19,786	—
Cost of monitoring	\$814	\$814
Cost of medications	\$1,096	\$1,245
Cost of reoperation	\$1,731	—
Cost of managing adverse events	\$71	—
Total costs	\$23,497 (\$22,044–\$25,287)	\$2,060
Life-years	4.63	4.63
QALYs	3.70 (3.48–3.89)	3.23 (2.65–3.74)
Incremental cost	\$21,438 (\$19,985–\$23,227)	
Incremental life-years	0.00	
Incremental QALYs	0.47 (0.10–0.90)	
ICER (cost/QALY)	\$45,817	

Abbreviations: MRgFUS, magnetic resonance-guided focused ultrasound; QALY, quality-adjusted life-year.

Research Question 2: What is the cost-effectiveness of MRgFUS neurosurgery compared with standard treatment (i.e., radiofrequency thalamotomy or deep brain stimulation) for people with moderate to severe, medication-refractory essential tremor, who are eligible for invasive neurosurgery, within the context of the Ontario Ministry of Health and Long-Term Care?

Table A12: Probabilistic Reference Case Analysis Results—Cost-Effectiveness of MRgFUS Neurosurgery, Radiofrequency Thalamotomy, and Deep Brain Stimulation

	MRgFUS, Mean (95% CI)	RF, Mean (95% CI)	DBS, Mean (95% CI)
Cost of primary surgery	\$19,786	\$11,774	\$37,366
Cost of monitoring	\$814	\$814	\$3,307
Cost of medications	\$1,096	\$1,096	\$1,081
Cost of reoperation	\$1,731	\$1,030	—
Cost of managing adverse events	\$71	\$259	\$6,306
Cost of battery replacement	—	—	\$9,463
Total cost	\$23,497 (\$22,044–\$25,287)	\$14,972 (\$14,096–\$16,051)	\$57,523 (\$55,507–\$59,772)
Life-years	4.63	4.63	4.63
QALYs	3.70 (3.48–3.89)	3.63 (3.42–3.82)	3.96 (3.75–4.14)

Abbreviations: AE, adverse events; DBS, deep brain stimulation; MRgFUS, magnetic resonance guided focused ultra sound; RF, radiofrequency.

Table A13: Probabilistic Reference Case Analysis Results—Incremental Cost-Effectiveness Ratios for MRgFUS Neurosurgery Versus Radiofrequency Thalamotomy or Deep Brain Stimulation

Intervention	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	Sequential ICER
Radiofrequency thalamotomy	\$14,972	3.63	—	—	—
MRgFUS neurosurgery	\$23,497	3.70	\$8,525	0.07	\$119,607
Deep brain stimulation	\$57,523	3.96	\$34,026	0.26	\$130,850

Abbreviations: ICER, incremental cost-effectiveness ratio; MRgFUS, magnetic resonance-guided focused ultrasound; QALY, quality-adjusted life-year.

Appendix 9: Letter of Information



LETTER OF INFORMATION

Health Quality Ontario is conducting a review of **magnetic resonance-guided focused ultrasound (MRgFUS)** treatment for patients with **essential tremor**. The purpose is to understand whether this therapy should be more broadly funded in Ontario.

An important part of this review involves speaking to patients and families of those who have experience with Essential Tremor, who may or may not have undergone MRgFUS treatment. Our goal is to make sure the experiences of patients and caregivers are considered in the funding recommendations for MRgFUS treatment for Essential Tremor.

WHAT DO YOU NEED FROM ME?

- ✓ 20-40 minutes of your time for a phone or in-person interview to share your story
- ✓ Permission to audio- (not video-) record the interview

WHAT YOUR PARTICIPATION INVOLVES

If you agree to share your experiences, you will be asked to have an interview with Health Quality Ontario staff. The interview will likely last 20-40 minutes. It will be held in a private location or over the telephone. With your consent, the interview will be audio-taped. The interviewer will ask you questions about you or your loved one's condition and your perspectives about essential tremor treatment options in Ontario. If you have undergone the MRgFUS procedure, the interviewer will ask some additional questions surrounding the procedure.

Participation is voluntary. You may refuse to participate, refuse to answer any questions or withdraw before your interview. Withdrawal will in no way affect care you receive.

CONFIDENTIALITY

All information collected for the review will be kept confidential and privacy will be protected except as required by law. The results of this review will be published, however no identifying information will be released or published. Any records containing information from your interview will be stored securely.

RISKS TO PARTICIPATION:

There are no known physical risks to participating. Some participants may experience discomfort or anxiety after speaking about their lived experience. If this is the case, please contact any staff.

If you are interested in participating, please contact Health Quality Ontario staff:

Appendix 10: Consent and Release Form

Consent and Release Form

This form is to be read and completed in accordance with the following instructions before it can be signed.

1. I, _____ allow Health Quality Ontario (Ontario Health Quality Council) to use to inform the development of an evidence based review:

Check off all appropriate boxes:

- a) ☐ a recording of my voice
b) ☐ a quotation or summary of my opinion that I expressed during an interview
c) ☐ name & contact information

2. Please read the following paragraphs before affixing your signature under section 3.

- a) Personal information collected pursuant to, and on this form, will be used for purposes described on this form and for no other purpose. Health Quality Ontario (Ontario Health Quality Council) acknowledges that you have provided this personal information freely and voluntarily. If you have any questions about this collection of this personal information, contact:
- b) By signing this form as indicated below, you agree to hereby release and forever discharge the Health Quality Ontario (Ontario Health Quality Council), its officers, employees, agents and representatives from any and all claims, demands, expenses, actions, causes of action and for any and all liability howsoever caused, arising out of, or in any way related to the collection, use and disclosure of information, recordings and images authorized to be collected pursuant to, or on this form.
- c) By signing this form as indicated below, you agree to forever waive any and all rights that you may have to the use of information and recordings that are authorized to be collected pursuant to, or on this form; and you acknowledge that all information, recordings and images shall hereafter remain the exclusive property of the Health Quality Ontario (Ontario Health Quality Council).

3. Signature is to be affixed in the appropriate space provided below.

I have read this form after it was completed, I understand and agree to be bound by its contents, and I am eighteen (18) years of age or over.

Signature _____

Print name _____

Date _____

Appendix 11: Interview Guide



Interview for MRgFUS HTA

Intro

Explain HQO purpose, HTA process, and purpose of interview
History of Essential Tremor - diagnosis and background (general only)

Lived- Experience

Day-to-day routine
What is the impact on quality of life?
Impact on loved ones/caregivers, work, etc.?

Therapies

What current therapies/treatments are used and their impact?
Is accessibility to therapies/treatments an issue (are you able to take advantage of all potential therapies?)
Expectations of current therapies?

MRgFUS

Information surrounding this procedure (or other surgical procedures)?
Decision-making for treatment. Was it difficult to weigh potential risks/benefits?
Expectations
Description of the procedure
Result, impact, change in quality of life

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About Health Quality Ontario

Health Quality Ontario is the provincial advisor on the quality of health care. We are motivated by a single-minded purpose: **Better health for all Ontarians.**

Who We Are.

We are a scientifically rigorous group with diverse areas of expertise. We strive for complete objectivity, and look at things from a vantage point that allows us to see the forest and the trees. We work in partnership with health care providers and organizations across the system, and engage with patients themselves, to help initiate substantial and sustainable change to the province's complex health system.

What We Do.

We define the meaning of quality as it pertains to health care, and provide strategic advice so all the parts of the system can improve. We also analyze virtually all aspects of Ontario's health care. This includes looking at the overall health of Ontarians, how well different areas of the system are working together, and most importantly, patient experience. We then produce comprehensive, objective reports based on data, facts and the voice of patients, caregivers and those who work each day in the health system. As well, we make recommendations on how to improve care using the best evidence. Finally, we support large scale quality improvements by working with our partners to facilitate ways for health care providers to learn from each other and share innovative approaches.

Why It Matters.

We recognize that, as a system, we have much to be proud of, but also that it often falls short of being the best it can be. Plus certain vulnerable segments of the population are not receiving acceptable levels of attention. Our intent at Health Quality Ontario is to continuously improve the quality of health care in this province regardless of who you are or where you live. We are driven by the desire to make the system better, and by the inarguable fact that better has no limit.

[About the Ontario Health Technology Advisory Committee \(OHTAC\)](#)

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Health Quality Ontario
130 Bloor Street West, 10th Floor
Toronto, Ontario
M5S 1N5
Tel: 416-323-6868
Toll Free: 1-866-623-6868
Fax: 416-323-9261
Email: EvidenceInfo@hqontario.ca
www.hqontario.ca

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