ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Magnetic Resonance-Guided Focused Ultrasound Neurosurgery for Treatment-Refractory Obsessive–Compulsive Disorder

A Health Technology Assessment

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Ontario Health

Key Messages

What Is This Health Technology Assessment About?

Obsessive–compulsive disorder (OCD) is a mental illness characterized by obsessions (recurring intrusive thoughts or images that cause anxiety) and/or compulsions (repetitive behavioural or mental rituals done in response to obsessions). For people living with OCD, the symptoms are very distressing and can take up many hours of the day, especially with severe OCD, which can prevent them from working or even caring for themselves.

Specialized therapy or medications can improve the symptoms of OCD. However, some people with OCD try many different types and combinations of these treatments with no meaningful improvement; this is considered treatment-refractory OCD. Neurosurgery (brain surgery) may be an option for people who have severe, treatment-refractory OCD. These surgeries are usually invasive (involve opening the skull) and can either ablate (destroy) or use electrical impulses to interrupt the brain circuits associated with OCD symptoms. Magnetic resonance-guided focused ultrasound (MRgFUS) is a technology that can be used to perform noninvasive (incisionless) neurosurgery for people with severe, treatment-refractory OCD and avoids the surgical risks of invasive procedures.

This health technology assessment looked at how safe and effective MRgFUS neurosurgery is for people with treatment-refractory OCD. It also looked at the budget impact of publicly funding MRgFUS neurosurgery and the experiences, preferences, and values of people with treatment-refractory OCD.

What Did This Health Technology Assessment Find?

MRgFUS neurosurgery may be an effective and generally safe treatment option for severe, treatment-refractory OCD, but the evidence is very uncertain.

We were unable to determine the cost-effectiveness of MRgFUS neurosurgery. We estimated that publicly funding MRgFUS neurosurgery for people with treatment-refractory OCD in Ontario would result in a total cost increase of $1.9 million over 5 years.

Patients who underwent MRgFUS neurosurgery commented on the positive impact that it had on their OCD symptoms, mental health, and quality of life. All patients and care partners emphasized the importance of having access to MRgFUS neurosurgery as a treatment option for treatment-refractory OCD.

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Abstract

Background

Obsessive–compulsive disorder (OCD) is a debilitating neuropsychiatric illness characterized by obsessions and compulsions that are distressing, impair function, and are time-consuming, especially in severe cases. Up to 40% of people with OCD have treatment-refractory OCD and experience inadequate response to multiple trials and combinations of treatments. Neurosurgery is an important treatment option for people with severe, treatment-refractory OCD but is typically invasive. Magnetic resonance-guided focused ultrasound (MRgFUS) is a noninvasive technology that is used to perform neurosurgery. We conducted a health technology assessment of MRgFUS neurosurgery for people with severe, treatment-refractory OCD, which included an evaluation of effectiveness, safety, the budget impact of publicly funding MRgFUS neurosurgery, and patient preferences and values.

Methods

We performed a systematic literature search of the clinical evidence published since 2013. We assessed the risk of bias of each included study using the Joanna Briggs Institute's Critical Appraisal Checklist for Case Series, 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 literature search of the economic evidence. We estimated the 5-year budget impact of publicly funding MRgFUS neurosurgery for people with treatment-refractory OCD in Ontario. Owing to a lack of comparative clinical evidence, we did not conduct a primary economic evaluation. To contextualize the value of MRgFUS neurosurgery, we spoke to people with treatment-refractory OCD who underwent the procedure, as well as those on the waitlist.

Results

We included 2 studies in the clinical evidence review. In these small case series, MRgFUS neurosurgery led to improvements in OCD symptoms, quality of life, and patient functioning, as well as treatment response for many but not all patients (GRADE: Very low). In a minority of cases, the procedure could not be successfully performed due to skull factors (GRADE: Very low). MRgFUS neurosurgery was also found to have a favourable safety profile (GRADE: Very low). No cases of re-treatment were reported (GRADE: Very low). No studies compared MRgFUS neurosurgery with other neurosurgeries.

Due to the lack of comparative clinical evidence, the cost-effectiveness of MRgFUS neurosurgery could not be determined. Our budget impact analysis found that publicly funding MRgFUS neurosurgery for people with treatment-refractory OCD in Ontario would cost an additional $1.9 million over 5 years.

Patients reported the negative impacts that OCD had on their day-to-day activities, work and school, social life and family relationships, and mental health. The 6 participants who underwent MRgFUS neurosurgery commented on the positive impact that it had on their OCD symptoms, mental health, and quality of life.

Conclusions

MRgFUS neurosurgery may be an effective and generally safe treatment option for severe, treatment-refractory OCD, but the evidence is very uncertain. The cost-effectiveness of MRgFUS neurosurgery could not be determined given the lack of comparative clinical evidence. Publicly funding MRgFUS neurosurgery for people with treatment-refractory OCD in Ontario would result in an additional cost of $1.9 million over 5 years. Patients and care partners emphasized the negative impact of OCD in their lives and highlighted the importance of having access to MRgFUS neurosurgery as a treatment option for treatment-refractory OCD.

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Objective

This health technology assessment evaluates the effectiveness and safety of magnetic resonance-guided focused ultrasound (MRgFUS) neurosurgery for people with treatment-refractory obsessive–compulsive disorder (OCD). It also evaluates the budget impact of publicly funding MRgFUS neurosurgery and the experiences, preferences, and values of people with treatment-refractory OCD.

Background

Health Condition

Obsessive–compulsive disorder (OCD) is a debilitating neuropsychiatric illness characterized by obsessions (recurrent, persistent intrusive thoughts or images that cause marked anxiety) and/or compulsions (repetitive behavioural or mental rituals performed in response to obsessions) that cause distress and functional impairment and are time-consuming.[1,2] Diagnosis often occurs in late childhood to early adolescence or in early adulthood, with most cases diagnosed before 30 years of age.[2-4] The symptoms of OCD tend to be episodic but chronic,[5] and additional psychiatric comorbidities (e.g., depression) are common.[2,4]

The lifetime prevalence of OCD for adults globally is approximately 1% to 2%, though it is likely underdiagnosed.[2,6] An analysis of data from the 2012 Canadian Community Health Survey – Mental Health measured the prevalence of OCD among people in Canada 15 years of age or older to be 0.93% (95% confidence interval, 0.75%–1.11%).[7] Symptoms, especially when severe, profoundly interfere with and negatively impact an individual's personal, social, and work lives, as well as those of their care partners.[2] The prevalence of suicide attempts among people with OCD has been estimated to be around 15%.[8] The severity of OCD symptoms is most commonly assessed by the Yale–Brown Obsessive–Compulsive Scale (Y–BOCS),[9] which scores severity as ranging from subclinical (i.e., Y–BOCS total severity score of 0 to 7), to mild (8 to 15), moderate (16 to 23), severe (24 to 31), and extreme (32 to 40) (scores above 15 are clinically significant).[10] In a US national survey, about half of people with OCD reported severe disability from their illness and another third reported moderate disability.[11]

Clinical Need and Population of Interest

The primary treatment for OCD is cognitive behavioural therapy (CBT) with OCD-specific protocols and exposure and response prevention (ERP) and pharmacotherapy (i.e., selective serotonin reuptake inhibitors [SSRIs]), delivered independently or in combination.[2] Although these constitute the most effective, evidence-based treatments,[4] about half of patients with OCD (30%–60%) do not experience partial or full response to first-line interventions (partial response and full response are defined as >25% to <35% reduction and ≥35% reduction in Y–BOCS total severity score, respectively).[12-16] Second-line or adjunctive pharmacologic agents (e.g., tricyclic antidepressants, serotonin–norepinephrine reuptake inhibitors, antipsychotics) may be trialled to augment primary treatment in cases with poor treatment response.[17] Various types of transcranial magnetic stimulation (TMS) (such as repetitive transcranial magnetic stimulation [rTMS] or deep transcranial magnetic stimulation [dTMS]) appear promising.[18,19] Some TMS devices hold regulatory approval for the treatment of OCD in select jurisdictions (e.g., US, some European countries, Canada); however, these treatments are currently not accessible in Canada.[19]

Other interventions, including transcranial direct current stimulation and electroconvulsive therapy, are generally not recommended, owing to a lack of compelling evidence for their use in treating OCD.[2,18-21] Despite the best combination of treatments, as many as 20% to 40% of people with OCD do not respond to second-line, third-line, or more treatments and remain severely ill and extremely impaired by their symptoms; this is referred to as treatment-refractory OCD. [5,14]

It is challenging to quantify how many people with OCD have treatment-refractory OCD, in part because less than half of people with OCD seek treatment.[2] There is also a lack of an operational definition for treatment-refractory or intractable disease[22]; however, the concepts are related and encompass elements of little or no symptom improvement or worsening symptoms, despite adequate trials of the best available and acceptable noninvasive treatments.[5,22-24]

Current Neurosurgery Options

Neurosurgery for severe, treatment-refractory OCD can use ablation (therapeutically destroying neural tissue and creating a lesion at the target brain structure or circuit) or deep brain stimulation (DBS; using electrical impulses to stimulate and disrupt brain activity in the target area). For both types of neurosurgery, the intention is to alter the structure and function of the brain to improve OCD symptoms by disrupting the underlying neural pathways.[14,17] The pathophysiology of OCD is not fully understood; however, the connections between the orbitofrontal cortex, anterior cingulate cortex, thalamus, and basal ganglia (i.e., cortico-striato-thalamo-cortical circuits), as well as dysfunction in serotonergic and glutamatergic systems, are strongly implicated.[4,7,23,25,26] DBS and ablative neurosurgery are stereotactic neurosurgeries, utilizing an external frame attached to the patient's head to enable very precise localization of brain targets, typically bilaterally (on both sides of the brain). The therapeutic effects of these procedures appear after a lag time of weeks or months; research suggests that the therapeutic effects may last for years after surgery.[27]

Neurosurgery for OCD should be provided only at specialty medical centres with an experienced multidisciplinary team and the necessary equipment.[24,28-30] Table 1 summarizes some of the considerations for any neurosurgery for OCD from organizations and entities that specialize in neurosurgery. Although treatment-refractory OCD is estimated to occur in a sizeable proportion of treatment-seeking people, a very small number fulfill additional eligibility criteria (e.g., duration of illness, functional impairment, acute suicidality, medical comorbidities) and are candidates for neurosurgery.[17] A longitudinal study on OCD in the US estimated that around 0.6% of treatment-seeking people with OCD may meet surgical eligibility criteria (i.e., severity, functional impairment, failure of sufficient treatment trials) for 1 type of neurosurgery, DBS.[17] A neurosurgeon in Ontario estimated, based on their clinical practice, that between 1 in 1,000 and 1 in 100 people with OCD who seek treatment could be refractory to nonsurgical treatments and be surgical candidates (A. Lozano, MD, PhD, virtual communication, June 6, 2023). Another neurosurgeon in Ontario estimated that one-third of people with severe, treatment-refractory OCD who would be eligible for intensive treatments (e.g., day programs or residential treatment) would be surgical candidates (N. Lipsman, MD, PhD, email communication, July 19, 2023).

Table 1: Summary of Considerations for Determining Eligibility and Suitability for Neurosurgical Intervention for Patients With OCD

Entity	Eligibility guidance	Additional considerations
Committee for Neurosurgery for Psychiatric Disorders, part of the World Society for Stereotactic and Functional Neurosurgery (WSSFN) and the European Society for Stereotactic and Functional Neurosurgery (ESSFN)[a] Consensus Guidelines[24]	• Severe, chronic, disabling disorder • Documented failure[b] or limited response to trials of adequate dose and duration of available standard therapies[c] • No reasonable, less-invasive, evidence-based therapy available • Little hope for spontaneous recovery • Promise of meaningful improvement	• Ability or capacity to give informed consent • Suicide risk • Cognitive abilities, psychiatric status, personality and interpersonal functioning, goals and expectations of surgery, treatment adherence, and level of family or other psychosocial support
Indian Psychiatric Society,[31] Indian Society for Stereotactic and Functional Neurosurgery, and The Neuromodulation Society Consensus Criteria 2019[29]	• Severe (Y–BOCS score ≥28 or ≥14 in case of illness with predominant obsessions or compulsions) and chronic OCD • Substantial distress and impairment in functioning (GAF ≤ 45) due to OCD • Lack of response to adequate and multiple trials of treatment options[d]	• Patient provides informed consent • Willingness to undergo preoperative evaluation and periodic postoperative follow-up • Presence of relative contraindications (e.g., comorbid intellectual disability, psychosis, unstable neurological conditions)
Royal College of Psychiatrists Position Statement 2017 (UK)[28]	• Treatment-refractory meeting consensus criteria for severity and refractoriness • Carefully selected with difficulty with OCD symptoms • Consider patient preference • Risks of neurosurgery versus risk of continuing "standard care"	• Special attention to patient advocacy, assess capacity, and gain informed consent • Explain to patients that neurosurgery is only 1 component of a broader, comprehensive treatment plan • Comprehensive postoperative follow-up and treatment plan (12 mo minimum)

Abbreviations: GAF, Global Assessment of Functioning; OCD, obsessive–compulsive disorder; Y–BOCS, Yale–Brown Obsessive–Compulsive Scale.

[a]Partnering with the working group "Deep Brain Stimulation in Psychiatry: Guidance for Responsible Research and Application", the Psychiatric Neurosurgery Committee of the American Society for Stereotactic and Functional Neurosurgery (ASSFN), the Latin American Society for Stereotactic and Functional Neurosurgery (SLANFE), the Asian-Australasian Society for Stereotactic and Functional Neurosurgery (AASSFN), and the World Psychiatric Association (WPA).

[b]Lack of efficacy or disabling side effects.

[c]For example, pharmacotherapy and behavioural therapy. As outlined by Visser-Vanderwalle et al[30]: "insufficient response to, at minimum: 2 selective serotonin reuptake inhibitors (SSRIs) at the maximum tolerated dose for at least 12 weeks; clomipramine at a maximum tolerated dosage for at least 12 weeks; 1 augmentation trial with an antipsychotic for at least 8 weeks, in combination with one of the aforementioned drugs; and a complete trial of exposure-based cognitive behavioural therapy (CBT) confirmed by a psychotherapist."

[d]Includes systematic treatment trials not discontinued prematurely due to mild side effects as follows: at least 3 months of ≥2 SSRIs and clomipramine, plus augmentation with at least 1 antipsychotic for at least 8 weeks and adequate trial of exposure and response prevention (ERP) CBT (≥20 sessions) or inability to tolerate the anxiety caused by therapy.[29]

Sources: Visser-Vanderwalle et al,[30] Nuttin et al,[24] Royal College of Physicians,[28] Doshi et al.[29]

The established surgeries have been found, mainly in small and often single-arm studies, to be clinically effective and safe for the treatment of OCD.[19,32] The surgeries offer different advantages and disadvantages resulting from the various approaches and mechanisms of action. Neurosurgery for OCD is not curative and should be part of a treatment plan that includes ongoing pharmacotherapy and/or psychotherapy to help patients manage their symptoms.

Ablative Neurosurgery

Ablative neurosurgery for psychiatric indications has existed since the 1940s.[14] There are a few surgical procedures that specify different neural pathways or targets, including cingulotomy (targeting the anterior cingulate cortex and cingulum), subcaudate tractotomy (targeting fibres below the caudate nucleus), limbic leucotomy (a combination of cingulotomy and subcaudate tractotomy), and anterior

capsulotomy (targeting the anterior limb of the internal capsule [ALIC]).[4,23] The most frequently performed procedures are capsulotomy and cingulotomy.[23]

Radiofrequency Ablation

Radiofrequency ablation (RFA) is the most established technique, with RFA anterior capsulotomy having the longest history of use. This type of open surgery involves a skin incision, cranial access through a burr hole in the skull, the insertion of very fine probes through the brain to the target area, and thermal ablation (permanent ablation of target tissue using heat). The lesion created is precise and develops immediately. This surgery is typically conducted under general anesthesia, but can be done under conscious sedation, and is associated with risks of invasive (open) surgery (e.g., infection, stroke, brain bleeding, brain swelling, wound complications, anesthesia complications) and may not be suitable for people on anticoagulant therapy. Clinical experts advised that RFA neurosurgery is the standard of care for patients with treatment-refractory OCD and is approved and available (covered by hospital global budget) in Canada. A 2016 systematic review found that RFA cingulotomy resulted in short- and long-term treatment response (partial or full) in 38% to 63% of patients with treatment-refractory OCD at 12 to 24 months after the procedure.[13] The rates of surgical complications (e.g., intracranial infection) are low (e.g., 1%–2%[23]), but transient cognitive effects or other adverse effects can occur in around 20% of cases (e.g., subjective memory issues, urinary incontinence).[13] Serious or permanent adverse effects following RFA capsulotomy or cingulotomy, such as memory or cognitive deficits, seizures, or personality changes, occur in around 2% to 5% of patients.[13,23]

Stereotactic Radiosurgery

Anterior capsulotomy can also be performed using stereotactic radiosurgery (focused radiation). Gamma Knife radiosurgery is a technique that delivers focused radiation through the intact skull to the target area of the brain. Unlike in RFA, where the lesion is created via craniotomy (opening the skull) immediately and precisely at the time of surgery, in radiosurgery the lesion develops gradually at the target site over time following surgery, taking up to several weeks or months to fully form. The irradiated area undergoes inflammatory changes and demyelination (damage of the insulating layer around nerves) of white matter tracts, with longer-term effects arising from the inability to produce certain neurotransmitters, thereby disrupting the targeted circuits.[27] For radiosurgical capsulotomy, the procedures are completed within a couple of hours, and the radiation dose delivered can range from 120 to 200 gray (Gy).[27] Gamma Knife stereotactic radiosurgery devices are approved by Health Canada (e.g., Leksell Gamma Knife, licence number 14773), and local experts advise that they are available and covered by hospital global budget for lesional neurosurgery in Canada. Gamma Knife radiosurgery for OCD may result in complete or partial response for about 60% to 70% of individuals.[23,27] Although craniotomy is not required and therefore this procedure does not hold the risks of open surgery, individuals are exposed to ionizing radiation, and the volume of the lesion is less predictable owing to the nature of radiation. As a result, the biological response to focused radiation can be idiosyncratic and difficult to predict, with some patients having no lesions and others having very large lesions. Transient adverse effects occur in most cases and can include vertigo, nausea or vomiting, and mild headaches.[13] Longer-term or permanent adverse effects can occur in 5% to 20% of people after Gamma Knife neurosurgery and may include radiation-induced cysts in the brain (which may be asymptomatic or cause neurological sequelae), weight gain, headaches, and loss of interest.[13,27,33]

Deep Brain Stimulation

DBS involves the semipermanent implantation of probes into the brain that are attached to a battery-operated neurostimulator (pulse generator) implanted subcutaneously (under the skin), near the clavicle (collarbone), chest, or belly.[34] The surgery is typically done in 2 stages: one surgery for the probes and another to implant the pulse generator. The optimal target for DBS in OCD is not yet known; however, common targets include the ALIC white matter tract, nucleus accumbens, subthalamic nucleus, and bed nucleus of the stria terminalis.[35] The advantages of DBS over ablative neurosurgery are its ability to be tailored to each individual and its potential reversibility.[36] The stimulation settings (i.e., amplitude, frequency, pulse width) can be adjusted to minimize side effects while maximizing the therapeutic effect on symptoms.[37,38] Probe implantation requires craniotomy, and one or both stages of the surgery may be done under general anesthesia, which bring unlikely but possible complications related to both procedures (e.g., infection, hemorrhage). In addition, there is device maintenance required over time (e.g., battery changes) and potential device-related complications (e.g., device malfunction, infection, pain at implantation site).[34] This surgery is not appropriate for people at elevated risk of infection, those taking anticoagulant therapy, or those with certain behaviours (e.g., skin picking, head banging).[32] In 2009, the US Food and Drug Administration (FDA) granted a Humanitarian Device Exemption (HDE 50003) to DBS in the ALIC for OCD, and in the same year, DBS for OCD was granted a CE mark in Europe.[39] According to clinical experts in this field in Ontario, DBS for OCD may be offered off-label under compassionate grounds and with clinical trial or philanthropic funds. DBS was first used for psychiatric indications in the late 1990s and has been demonstrated to be effective and cost-effective for treatment-refractory OCD, with studies reporting that around 60% to 75% of patients experience clinical response (i.e., Y–BOCS score reduced by ≥35%)[40,41] and incremental cost-effectiveness ratios (ICERs) in UK-, Korea-, and Netherlands-based analyses are around $35,000 USD to $65,000 USD per quality-adjusted life-year (QALY) gained relative to nonsurgical therapy.[41]

Health Technology Under Review

Magnetic resonance-guided focused ultrasound (MRgFUS) is a thermal ablation technology consisting of a special ultrasound transducer helmet, a specialized control console, and real-time magnetic resonance imaging (MRI). It is a noninvasive technique for ablative neurosurgery that uses sound waves to generate precise, targeted lesions in the key brain circuits implicated in OCD. Ultrasound waves are emitted through the intact skull, and when they converge at the focal point, the target brain tissue is heated and ablated (focal coagulative necrosis). The patient's head must be completely shaved and have a stereotactic frame attached. During the procedure, real-time MRI provides detailed images of the brain, allowing for a high degree of precision and minimizing the risk of damage to surrounding tissue.[42] Real-time feedback of thermal data throughout the procedure allows the clinical team to precisely adjust the location and temperature parameters.[42]

MRgFUS can be used to perform capsulotomy instead of a traditional open surgical approach. The procedure takes 2.5 to 4 hours and is completed entirely in the MRI suite, with patients awake. Although an anesthetist is typically present, it is done without the need for general anesthesia. Because MRgFUS takes place inside an MRI machine, this procedure cannot be done if an individual has contraindications to MRI such as incompatible implanted medical devices or body size. The manufacturer notes that the device should not be used for people with substance abuse disorders, renal disease, pregnancy, contrast agent allergies, or cerebrovascular disease.[42] Ultimately, it is the joint decision of the neurosurgeon and psychiatrist whether it is appropriate to offer MRgFUS to a patient. In addition, a high skull-density ratio (≥0.40, assessed by brain computed tomography) is key to achieving therapeutic temperature (i.e., to

ablate tissue) and is associated with lesion efficacy,[43] although a sufficient lesion may still be achieved in patients with less favourable skull densities. MRgFUS forgoes the risks associated with open surgery and provides an option for people who cannot have general anesthesia. It can also provide a treatment option for people with traditional surgical contraindications and people who find invasive procedures, ionizing radiation, or the associated risks unacceptable.

Regulatory Information

The Exablate Neuro (or Exablate 4000; Insightec Ltd) is the only commercially available MRgFUS system for neurological indications. It consists of a piezoceramic helmet transducer with a phased array of 1,024 rays (at 650 Hz) and specialized algorithms to ensure that the beams reach the target, and is compatible with 1.5T and 3T MRI machines.[42] The device holds active Health Canada licences as a Class III device (licence numbers 96969 and 103423), as well as regulatory approval from several other jurisdictions. In Canada, OCD is not an approved intended use for the Exablate Neuro; the Exablate Neuro is currently intended for use in the unilateral treatment of refractory essential tremor (thalamotomy) in patients 22 years of age or older.[44] Thalamotomy with MRgFUS has been recommended and publicly funded for essential tremor in Ontario since 2018.[45,46] Internationally, the intended uses are mainly for movement disorders (e.g., essential tremor, Parkinson's disease) and neuropathic pain (Appendix 1, Table A1). South Korea is the only jurisdiction that mentions behavioural disorders when describing the intended uses of the device.

Ontario, Canadian, and International Context

Ontario and Canada

MRgFUS neurosurgery for OCD requires highly specialized, multidisciplinary clinical teams. At the time of writing, we are aware of 4 sites in Canada with the expertise and equipment required to perform MRgFUS neurosurgery: 1 in Calgary, Alberta; 1 in Montreal, Quebec; and 2 in Toronto, Ontario. One of the sites in Ontario has treated patients with movement disorders, including essential tremor, Parkinson's disease, and dystonia (A. Lozano, MD, PhD, virtual communication, June 6, 2023). The other site in Ontario has assessed many patients with severe, treatment-refractory OCD who are eligible for surgical intervention and has treated some carefully selected patients with MRgFUS, first in the context of a phase I research study (n = 12),[47] and subsequent patients have received treatment with support from philanthropic funds. The Exablate Neuro is being used (off-label) under humanitarian and compassionate grounds, obviating the need for an operating room procedure and the risks of open surgery (N. Lipsman, MD, PhD, virtual communication, July 22, 2022).

Referrals for potential candidates for MRgFUS neurosurgery in Ontario can be sent by any physician, including a family doctor, but in most cases a treating psychiatrist makes the referral. Individuals then undergo screening by a multidisciplinary team. The screening process aims to determine the suitability and safety of MRgFUS for an individual patient. People with severe, treatment-refractory OCD must have a primary diagnosis of OCD and are carefully screened for comorbidities that may make them ineligible (e.g., substance abuse disorder, psychosis).

If initial eligibility is met, the individual then undergoes psychiatric assessment by 2 independent psychiatrists, who must independently conclude and agree that it is appropriate to proceed with a neurosurgical consultation. If the individual is deemed a suitable candidate for MRgFUS neurosurgery by the neurosurgeon, the procedure is scheduled, and the individual undergoes preoperative assessment,

including brain imaging, bloodwork, neuropsychologic assessment, and other appropriate tests. This is similar to the process for any psychiatric neurosurgery. The time from referral to MRgFUS procedure is estimated to be 6 to 8 months (A. Baskaran, PhD, virtual communication, May 26, 2023). Since 2017, the 1 site in Ontario that offers MRgFUS neurosurgery has provided treatment for 32 carefully selected patients with OCD from Ontario and across Canada (as of December 14, 2023), with about 1 patient per month undergoing MRgFUS (A. Baskaran, PhD, email communication, December 14, 2023). The volumes to date are based on a balance of the need for MRgFUS with the site's capacity to treat based on clinical and human resources (e.g., MRgFUS suite availability, MRI time, surgeon time and scheduling) (N. Lipsman, MD, PhD, virtual communication, May 26, 2023).

The University of Calgary–affiliated site in Alberta lists essential tremor and OCD (bilateral capsulotomy) as indications for MRgFUS neurosurgery.[48] According to the Focused Ultrasound Foundation, this is provided in the context of clinical research.[49] The Montreal Neurological Institute and Hospital site treats only essential tremor with MRgFUS.[49]

International

Most international guidelines do not provide any recommendations about the use of MRgFUS for treatment-refractory OCD, except the 2023 guideline from the World Federation of Societies of Biological Psychiatry[18] (see Table 2). In 2021, the National Evidence-based Healthcare Collaborating Agency in South Korea assessed the safety and effectiveness of MRgFUS for neurosurgical indications, including treatment-refractory OCD.[50] The clinical systematic review results were examined by the New Health Technology Assessment (nHTA) Committee in South Korea, which concluded that further research was required to determine safety and effectiveness in improving symptoms.[50] Ablative neurosurgery with MRgFUS for OCD is available at Yonsei University Health System, Severance Hospital in South Korea.[51] The National Institute for Health and Care Excellence (NICE) guideline has not been updated since 2005 and does not recommend ablative neurosurgery for severe, chronic, treatment-resistant OCD unless requested by the patient.[21] All more-recent guidelines state that DBS or ablative neurosurgeries can be considered as last resorts for treatment-refractory OCD (Table 2).

Table 2: Summary of Recommendations for Neurosurgeries for Treatment-Refractory OCD

Entity (jurisdiction)	Recommendation	Source(s)
American Psychiatric Association (US)	Ablative neurosurgery for severe, treatment-refractory OCD is rarely indicated and, along with DBS, should be performed only at sites with expertise in both OCD and these treatment approaches	American Psychiatric Association, 2007[52,53]
Canadian clinical practice guidelines (Canada)	**Ablative neurosurgery** Capsulotomy or cingulotomy may be effective in reducing symptoms in patients with severe, treatment-refractory OCD; however, these treatments are usually considered last resorts	Katzman et al, 2014[2]
	DBS DBS may improve symptoms and functionality in up to two-thirds of patients with highly treatment-refractory OCD	Katzman et al, 2014[2]
Congress of Neurological Surgeons and the American Society for Stereotactic and Functional Neurosurgery (US)	**DBS** Bilateral subthalamic nucleus DBS is recommended for medically refractory OCD, above best medical management; bilateral nucleus accumbens or BNST DBS may also be used	Staudt et al, 2021[54]
Indian Psychiatric Society (India)	**Ablative neurosurgery/DBS** Can be recommended for carefully selected patients with treatment-refractory OCD after discussing the pros and cons	Janardhan Reddy et al, 2017[31]
NICE (UK)	**Ablative neurosurgery** Not recommended for severe, chronic, treatment-resistant OCD unless a patient requests it; many considerations and due processes	NICE, 2005[21,a]
	DBS DBS for chronic, severe, treatment-resistant OCD in adults should be done only in the context of research	NICE, 2021[55]
Royal College of Psychiatrists Position Statement (UK)	**Ablative neurosurgery** Anterior capsulotomy and anterior cingulotomy are considered part of acceptable, safe, effective, and established clinical practice in the UK for chronic, otherwise treatment-refractory OCD	Royal College of Psychiatrists, 2017[28]
	DBS Should be considered investigational and be used only within a research protocol that has full ethics approval	Royal College of Psychiatrists, 2017[28]
World Federation of Societies of Biological Psychiatry (International)	**Ablative neurosurgery** RFA, Gamma Knife, and MRgFUS should be restricted to carefully selected patients with treatment-refractory OCD	Bandelow et al, 2023[18]
	DBS DBS should be restricted to carefully selected patients with treatment-refractory OCD	Bandelow et al, 2023[18]

Abbreviations: BNST, bed nucleus of the stria terminalis; DBS, deep brain stimulation; MRgFUS, magnetic resonance-guided focused ultrasound; NICE, National Institute for Health and Care Excellence; OCD, obsessive–compulsive disorder; RFA, radiofrequency ablation.

[a]Evidence update completed in 2013; no new evidence was identified relevant to intensive or inpatient treatments for OCD.[20]

Individual Preferences for Neurosurgery

Whether a person receives ablative neurosurgery or DBS depends on many factors beyond medical and psychiatric suitability. For example, there may be a strong preference for a single ablative procedure or a minimally invasive approach with radiosurgery, or varying acceptability of implants in the body. There is

also consideration of accessibility to highly specialized centres, given that DBS requires many follow-up visits after surgery to learn how to use the device and adjust the settings.[32]

People who underwent neurosurgical intervention, such as DBS, for treatment-refractory OCD have reported marked improvement in symptoms and satisfaction with their procedure.[56] In feedback collected from patients, they noted that their symptoms and function improve considerably, they are satisfied with DBS as a treatment, and they rate their quality of life as better following surgery and fine-tuning of DBS settings.[56] People with OCD who underwent DBS recommended improving the awareness and availability of DBS as a treatment option.[56] Some patients and members of the medical community may be hesitant about neurosurgical treatment for OCD; this stems from other historical psychiatric surgeries (e.g., lobotomy) that do not resemble modern neurosurgical techniques.[32]

Equity Context

It is well documented that people with OCD experience a variety of complex issues and are far more likely than the general population to report needing psychological help and not receiving it.[7] People with severe OCD experience stigma and discrimination in addition to severe illness, which compounds poor quality of life, social exclusion, and low self-esteem.[57,58] In Canada, people with OCD are more likely to have lower income or live in rural areas, and are less likely to be employed.[7] There is also a slightly higher prevalence of OCD among females than males (1.04% versus 0.81%).[7] Although the prevalence of OCD is slightly higher among females and there are some socioeconomic and demographic trends among people with OCD compared with the general population, no specific subgroup or population was identified that would likely benefit more from this intervention over another.

Therefore, if MRgFUS neurosurgery for treatment-refractory OCD is funded and implemented in Ontario, it is not expected that it would contribute to inequality among people with different equity factors; rather, it is expected that public funding could improve equity through improved access for people who do not want or cannot undergo invasive ablative surgery, or who are waiting long durations with substantial distress and disability due to surgical wait times and backlog. Public funding and implementation will expand access to a last-line treatment option that can positively impact patient quality of life.

Expert Consultation

We engaged with clinical experts in the specialty areas of neurosurgery and psychiatry to help inform our understanding of aspects of the health technology and our methodologies and to contextualize the evidence.

PROSPERO Registration

This health technology assessment has been registered in PROSPERO, the international prospective register of systematic reviews (CRD 42023457743), available at crd.york.ac.uk/PROSPERO.

Clinical Evidence

Research Question

What are the effectiveness and safety of magnetic resonance-guided focused ultrasound (MRgFUS) neurosurgery for the treatment of people with treatment-refractory obsessive–compulsive disorder (OCD)?

Methods

Clinical Literature Search

We performed a clinical literature search on August 14, 2023, to retrieve studies published from January 1, 2013, until the search date, given that the phase I trials of the Exablate Neuro were published in 2013. We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the National Health Service Economic Evaluation Database (NHS EED), and APA PsycInfo.

A medical librarian developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. The final search strategy was peer-reviewed using the PRESS Checklist.[59]

We created database auto-alerts in MEDLINE, Embase, and APA PsycInfo and monitored them until November 14, 2023. We also performed a targeted grey literature search of the International HTA Database, the websites of health technology assessment organizations and regulatory agencies, and clinical trial and systematic review registries, following a standard list of sites developed internally. See Appendix 2 for our literature search strategies, including all search terms.

Eligibility Criteria

Studies

Inclusion Criteria

- English-language full-text publications
- Studies published since January 1, 2013
- Comparative (randomized or nonrandomized) or single-arm cohort studies, case series, and case reports
    - Case reports were excluded if case series were identified, given that the latter have greater potential for statistical power and external validity to inform conclusions and evidence-based recommendations
- Systematic reviews (including meta-analyses and health technology assessments that include a systematic review) that match our research question and inclusion criteria

- Systematic reviews must clearly report literature search methods, including (at a minimum) information about the databases searched, search terms, and search dates
- Systematic reviews that have a broader scope must also report separate patient characteristics, methods, results, and critical appraisal for our population, intervention, comparators, and outcomes (PICO) in sufficient detail

Exclusion Criteria

- Editorials, commentaries, narrative reviews, conferences abstracts, posters, letters, and preprints
- Non-English full-text reports and publications
- Studies with broader or diverse populations from which participant characteristics, methods, and results for those with OCD cannot be extracted
- Proof-of-concept, feasibility, or technical validation studies (i.e., not clinical application)
- Animal and in vitro studies

Participants

Inclusion Criteria

- Adults (≥18 years old) with severe, treatment-refractory OCD, as defined by the study (e.g., treatment failures, severity according to Yale–Brown Obsessive–Compulsive Scale [Y–BOCS] total severity score, Clinical Global Impression [CGI] score, clinical judgement of patients' functional limitations)

Exclusion Criteria

- Mild or moderate OCD, presence of psychotic symptoms in the past or present, active severe substance abuse, comorbid dementia or neurodegenerative disorders

Interventions

Inclusion Criteria

- MRgFUS psychiatric neurosurgery, with or without co-interventions (such as psychotherapy and/or pharmacotherapy)
    - Anterior capsulotomy, anterior cingulotomy, caudate tractotomy, or limbic leukotomy (bilateral or unilateral)

Exclusion Criteria

- Other brain targets or neurosurgeries

Comparators

Inclusion Criteria

- Radiofrequency ablation (RFA), with or without co-interventions (such as psychotherapy and/or pharmacotherapy)
- Gamma Knife radiosurgery, with or without co-interventions (such as psychotherapy and/or pharmacotherapy)
- Deep brain stimulation (DBS) , with or without co-interventions (such as psychotherapy and/or pharmacotherapy)
- No comparator

Exclusion Criteria

- Nonsurgical treatments (e.g., deep transcranial magnetic stimulation [dTMS], pharmacotherapy, cognitive behavioural therapy [CBT], exposure and response prevention [ERP] therapy, intensive inpatient treatment)

Outcome Measures

- OCD symptoms, for example:
  - Change in Y–BOCS or Clinical Global Impression – Improvement (CGI–I) scores
  - Partial or complete response (e.g., >25% to <35% reduction or ≥35% reduction Y–BOCS score, respectively)
  - Clinical remission (e.g., ≥55% improvement of Y–BOCS score, Y–BOCS score < 7)
- Adverse effects and events
- Neurocognitive changes (e.g., personality changes)
- Technical failure (e.g., unable to achieve therapeutic temperature, patient cannot tolerate head frame or sonications during procedure)
- Follow-up interventions or re-treatment
- Patient quality of life (e.g., functionality)
- Patient satisfaction

Literature Screening

Two reviewers screened titles and abstracts to assess the eligibility of a sample of 100 citations to validate the inclusion and exclusion criteria. Ninety-percent agreement was reached prior to discussing conflicts, after which 100% agreement was confirmed. One reviewer then screened all remaining citations using Covidence systematic review management software[60] and obtained the full texts of studies that appeared eligible for the review, according to the inclusion criteria. The same reviewer then examined the full-text articles and selected studies eligible for inclusion. The reviewer also examined

reference lists of all identified systematic reviews and all included studies for any additional relevant studies not identified through the search, and consulted clinical experts for feedback on omissions regarding pivotal studies. Citation flow and reasons for exclusion for full-text articles are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[61]

Data Extraction

We extracted relevant data on study design and characteristics; risk-of-bias items; results; and population, intervention, comparator, outcome, time, and setting (PICOTS) using a data form to collect information on the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, study duration and years, participant allocation, allocation sequence concealment, blinding, reporting of missing data, reporting of outcomes, whether the study compared 2 or more groups)
- Outcomes (e.g., outcomes measured, number of participants for each outcome, number of participants missing for each outcome, outcome definition and source of information, unit of measurement, time points at which the outcomes were assessed)

Where multiple articles reported on the same outcomes and patients, we extracted data from the most comprehensive and recent publication(s), supplemented with information from others as needed.

Equity Considerations

We used the PROGRESS-Plus framework to help explicitly consider health equity in our health technology assessment.[62] PROGRESS-Plus is a health equity framework used to identify population and individual characteristics across which health inequities may exist. These characteristics include place of residence; race or ethnicity, culture, or language; gender or sex; disability; occupation; religion; education; socioeconomic status; social capital; and other key characteristics (e.g., age) that may stratify health opportunities and outcomes. Potential equity issues related to the research question were not evident during scoping. However, we report the available characteristics of participants in the included studies (e.g., PROGRESS-Plus categories).

Statistical Analysis

For cases in which information about people with OCD was combined with that of other patient populations, we calculated measures of central tendency and descriptive statistics (e.g., mean, standard deviation) for people with OCD only from the data available in the published articles and supplementary materials.

One reviewer assessed for the presence and extent of statistical, methodological, and clinical heterogeneity and considered this when interpreting the results.[63] We did not perform a meta-analysis given the very low number of studies and methodological diversity between studies.[64,65] Therefore, results are summarized using structured tabulation[66] and narrative summaries.

Critical Appraisal of Evidence

We assessed risk of bias using the Joanna Briggs Institute's Critical Appraisal Checklist for Case Series[67] (Appendix 3).

We evaluated the quality of the body of evidence for each outcome according to the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) *Handbook*.[68] The body of evidence was assessed based on the following considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall rating reflects our certainty in the evidence.

Results

Clinical Literature Search

The systematic search of the clinical literature yielded 275 citations published between January 1, 2013, and August 14, 2023, including grey literature and after duplicates were removed. We did not identify any additional eligible studies from other sources, including database alerts (monitored until November 14, 2023). We identified 3 systematic reviews[14,69,70] that were ineligible; specifically, they did not match our research question, did not provide adequate literature search details, or the literature search was outdated (e.g., missing the most recent studies published). As per our protocol, single case reports were excluded given that larger case series were identified. One case report[71] was also subsumed in a publication of a case series[72]; therefore, the individual report was excluded. See Appendix 4 for a list of selected studies excluded after full-text review. We included 2 primary studies (case series) reported in 8 publications.[72-79] Figure 1 presents the PRISMA flow diagram for the clinical literature search.

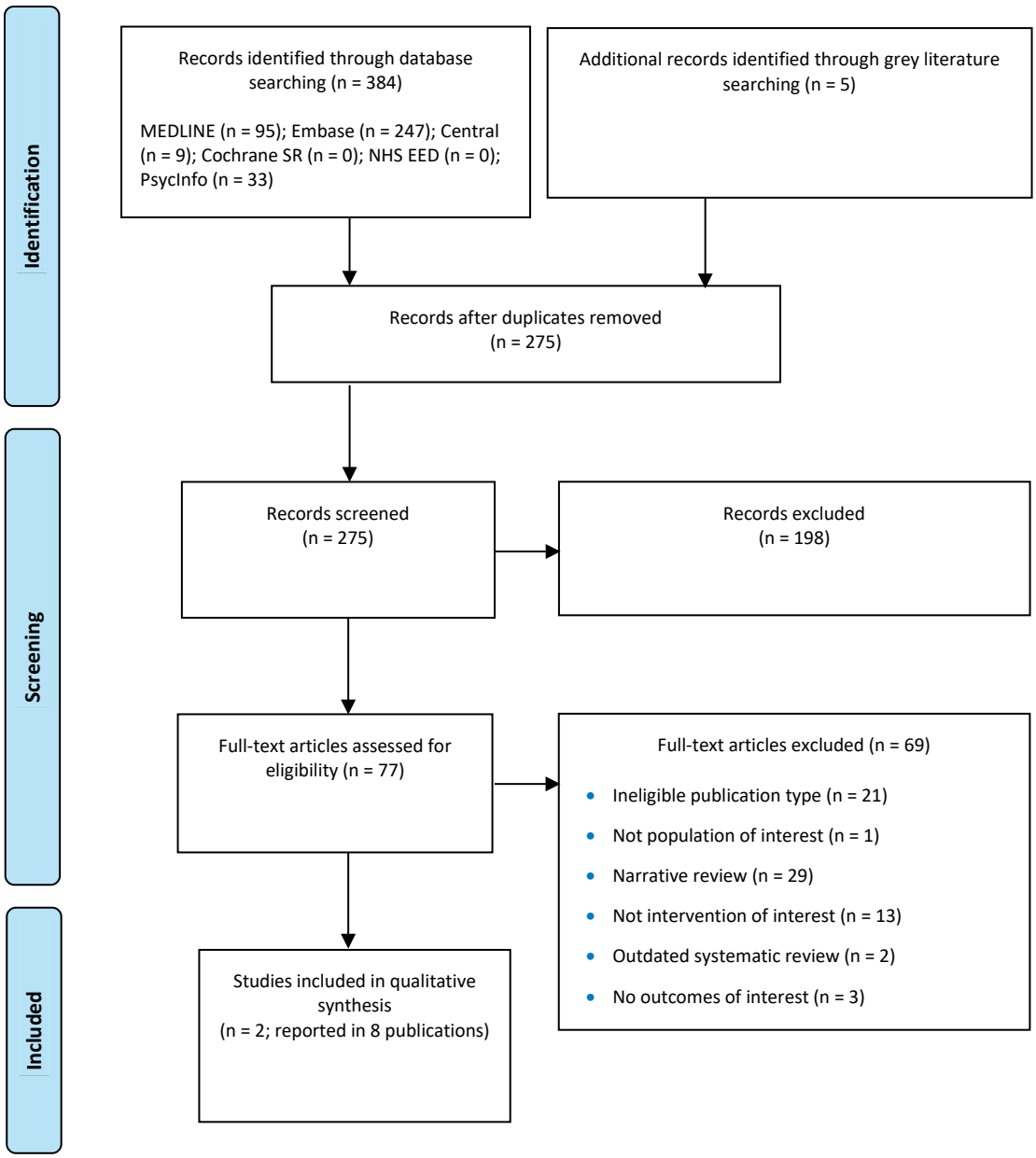

Figure 1: PRISMA Flow Diagram – Clinical Systematic Review

PRISMA flow diagram showing the clinical search strategy. The search of the clinical literature yielded 275 citations published between January 1, 2013, and August 14, 2023, including grey literature searches and after duplicates were removed. We screened the abstracts of the 275 identified studies and excluded 198. We assessed the full text of 77 articles and excluded a further 69. In the end, we included 2 articles in the qualitative synthesis.

Abbreviations: Cochrane SR, the Cochrane Database of Systematic Reviews; NHS EED, National Health Service Economic Evaluation Database; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Source: Adapted from Page et al.[61]

Characteristics of Included Studies

We included 2 studies that examined MRgFUS capsulotomy in patients with severe, treatment-refractory OCD. One study was conducted in Canada[72] and the other in South Korea,[79] and both registered protocols on clinical trial registries.

The study conducted in South Korea published 2 articles on subsets of study participants, including preliminary clinical findings[78] and an analysis of neural oscillation patterns after the procedure.[73] However, no outcome data from these publications are reported, given that it was only a subset of all patient data and another publication reported outcomes of the entire case series.[79] The Canadian researchers reported results of the clinical trial on MRgFUS for OCD along with a second trial of the same intervention for patients with treatment-refractory major depressive disorder.[72] Therefore, we separated and reported only on the characteristics, procedural information, analysis, and results of patients with OCD as available from the published article and supplementary materials.

The clinical and demographic characteristics of study participants are presented in Table 3. These open-label case series prospectively followed patients with treatment-refractory OCD who did not respond to multiple trials of pharmacologic and cognitive-behavioural therapies and underwent MRgFUS capsulotomy. To be eligible for MRgFUS, individuals were required to have a primary diagnosis of OCD with a minimum duration of 3 to 5 years and a Y–BOCS score of 28 or greater (i.e., severe OCD). There was 1 exception to this score cut-off in the Canadian study; the authors state that 1 person was treated outside the clinical trial, on humanitarian grounds, given that they were substantially impaired despite not meeting the Y–BOCS criteria (i.e., score of 23 arising from their OCD manifesting with minimal compulsions).[72]

MRgFUS neurosurgery was performed in a 3T MRI using the Exablate Neuro system (Insightec Ltd, Haifa, Israel). The surgical target was the anterior limb of the internal capsule (ALIC), and capsulotomy was performed bilaterally. In the Canadian study, the procedure lasted 3 to 4 hours[72] and was performed under conscious sedation (e.g., low-dose propofol or dexmedetomidine[74]) to ensure patients were more comfortable, especially during the high-energy sonications. Nasal oxygen was also provided to patients during the procedure, and all patients underwent postoperative imaging to examine the lesion. In the South Korean study, patients were fully awake and responsive throughout the 5- to 7-hour MRgFUS procedure, underwent postprocedure MRI scans, and were monitored as inpatients for 24 hours, then every 2 to 4 weeks at outpatient psychiatric clinic visits.[78]

Neither study provided CBT or ERP therapy as a co-intervention after MRgFUS neurosurgery, but in 1 study, patients were reminded of the techniques they had learned by psychiatrists at follow-up visits during the study.[78] In both studies, patients were required to be on a stable medication regimen (i.e., no changes) for at least 30 days prior to MRgFUS capsulotomy. In the South Korean study,[79] all patients continued to take their previous medication regimen and dosage throughout the entire 2-year study period,[77] whereas in the Canadian study, although patients were encouraged to continue on the same medications and doses in the postoperative period, medication changes occurred at the discretion of the treating psychiatrist; only 2 of the participants did not have any medication changes during the follow-up period.[72]

There was no information reported in either study about study participants' race, ethnicity, culture, place of residence, socioeconomic status, occupation or work arrangements, gender identity, sexual orientation, religion, educational level, social capital, or disabilities.

Table 3: Characteristics of Studies Included in the Clinical Systematic Review

	Study design				Participants				
Author, year, country	Study type	Procedure (brain target)	Follow-up	Outcomes of interest	Population	Sample size, N (n with psychiatric comorbidity)	Duration of OCD, mean (range), y	Age, mean (SD), y	Sex, M:F
Davidson et al, 2020,[72,74-76] Canada	Prospective, open-label case series	Bilateral MRgFUS capsulotomy using Exablate Neuro (ALIC)	6–12 mo[a]	Y–BOCS score Adverse events Neurocognitive test results Technical failure Quality of life Follow-up interventions	Primary diagnosis of OCD (DSM-V) and minimum illness duration of 5 y, Y–BOCS score ≥ 28 and refractory to • ≥3 trials of antidepressants • >2 trials of drug augmentation or combination • ≥1 trial of psychotherapy	6[a] (4[a])	14.5 (6–24) Median, 13	31 (4.7[b]) Median, 31	3:3
Kim et al, 2018,[73,77-79] South Korea	Prospective, open-label case series	Bilateral MRgFUS capsulotomy using Exablate Neuro (ALIC)	2 y	Y–BOCS score CGI score Global functioning Adverse events Technical failure Follow-up interventions	Primary diagnosis of OCD (DSM-IV) and more than 5 y of symptoms and dysfunction, Y–BOCS score ≥ 28 and refractory to • >3 SSRIs at maximum tolerated dose for >12 wk • >1 antipsychotic augmentation • 20+ sessions of CBT-ERP	11 (7)	14.6 (9–24) Median, 13	32 (8.1) Median, 34	5:6

Abbreviations: ALIC, anterior limb of the internal capsule; CBT, cognitive behavioural therapy; CGI, Clinical Global Impression; DSM, *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV, 4th edition; DSM-V, 5th edition); ERP, exposure and response prevention; F, female; M, male; MRgFUS, magnetic resonance-guided focused ultrasound; OCD, obsessive–compulsive disorder; SD, standard deviation; SSRI; selective serotonin reuptake inhibitor; Y–BOCS, Yale–Brown Obsessive–Compulsive Scale.

[a]Number of patients with OCD. Nine patients with OCD were enrolled; 1 was excluded after consent but before MRgFUS. Of the 8 patients with OCD for whom MRgFUS was attempted, the procedure was not completed in 2 cases, and information on the characteristics of these 2 patients is not available.[72] One additional patient was treated after March 2019 but before December 2019 and had not reached 6 months of follow-up as of September 2019 when analysis was conducted.[74]

[b]Calculated from data on 6 patients with OCD available in the publication and its published supplementary material.[72]

Risk of Bias in the Included Studies

The detailed results of the risk-of-bias assessment are presented in Appendix 3, Table A2.[67] There were some unclear aspects related to the selection of participants, complete inclusion of cases,[72,79] and inclusion of consecutive cases.[72] The demographic characteristics of study participants were partially unclear.[72,79]

OCD Symptoms

Y–BOCS Score

The studies assessed the severity of OCD symptoms at baseline and throughout follow-up. Both studies[72,79] assessed the Y–BOCS score of most or all patients at 1, 3, 6, and 12 months after the procedure, and Kim et al[79] assessed Y–BOCS additionally at 1 week and 24 months. In the study by Davidson et al,[72] a Y–BOCS score was not available for all 6 patients at each follow-up time point; 1 patient was treated outside of the clinical trial and another had not yet reached 12 months of follow-up (Table 4).

The numeric value of the Y–BOCS scores decreased at every follow-up in both studies (Table 4), indicating an improvement in OCD symptoms. Kim et al[79] analyzed the change in Y–BOCS score with a linear mixed model for repeated measures and found a statistically significant decrease in mean scores over the follow-up period ($P < .001$). Statistically significant improvement from baseline was seen as early as 1 week after the procedure ($P = .03$), and scores continued to improve at every follow-up visit (statistically significant, $P < .05$ for all; post hoc analysis with Bonferroni correction).[79]

Using a linear mixed model for repeated measures, Kim et al[79] reported that Y–BOCS scores decreased over the 24-month follow-up; this decrease was statistically significant ($P < .001$). Compared with baseline, improvements in OCD symptoms were seen starting as early as 1 week after the procedure ($P = .035$) and at each time point thereafter ($P < .05$ for all, in the post hoc analysis for changes from baseline with Bonferroni corrections).[79]

The reductions in mean Y–BOCS scores (Table 4) translated into changes in symptom severity[10] from extreme at baseline, to severe during approximately the first 6 months, to moderate at the end of follow-up.

Davidson et al[72] reported the mean change in Y−BOCS score before and after the procedure. This was analyzed at the last available follow-up for each patient; for 4 patients, this was at 12 months, and for the other 2 patients, this was at 6 months, as they had not yet reached 12 months since MRgFUS capsulotomy. Across the patients with OCD, the mean percent change in Y–BOCS score at last follow-up was a statistically significant reduction of 33.3% ($P = .03$; Table 5).[72] The percent change (reductions) from baseline to the 6-, 12-, and 24-month follow-ups in the study by Kim et al[79] were numerically similar to those in the study by Davidson et al[72] (Table 5).

The GRADE quality of the evidence was rated as Very low, given limitations related to imprecision (Appendix 3, Table A3).

Table 4: Y–BOCS Score Over Time Before and After MRgFUS Capsulotomy

		Y–BOCS score, mean, SD (n)						
Author, year	**Country**	**Baseline**	**1 wk**	**1 mo**	**3 mo**	**6 mo**	**12 mo**	**24 mo**
Davidson et al, 2020[72]	Canada	33, 7.6 (6)	NA	29.8, 3.1 (5)	28.6, 5.7 (5)	25.8, 8.6 (6)	20, 2.1 (4)	NA
Kim et al, 2018[79]	South Korea	34.4, 2.3 (11)	30.3,[a] 4.3 (11)	28.2,[b] 4.6 (11)	25.9,[b] 4.2 (11)	23.6,[b] 4.5 (11)	21.8,[b] 4.8 (11)	21.3,[b] 6.2 (11)

Abbreviations: MRgFUS, magnetic resonance-guided focused ultrasound; NA, not assessed at this time point; SD, standard deviation; Y–BOCS, Yale–Brown Obsessive–Compulsive Scale.

[a]Statistically significant change from baseline ($P = .035$) in post hoc analysis with Bonferroni correction.[79]

[b]Statistically significant change from baseline ($P < .05$) in post hoc analysis with Bonferroni correction.[79]

Table 5: Change in Y–BOCS Score from Baseline After MRgFUS Capsulotomy

Author, year	**Time point**	**Mean change from baseline, % (SD)**	***P* value**
Davidson et al, 2020[72]	Last follow-up[a]	−33.3 (NR)	.03
Kim et al, 2018[79]	6 mo	−31.1 (13.3)	NR
	12 mo	−36.1 (15.3)	NR
	24 mo	−37.8 (18.9)	NR

Abbreviations: MRgFUS, magnetic resonance-guided focused ultrasound; NR, none reported; SD, standard deviation; Y−BOCS, Yale−Brown Obsessive–Compulsive Scale.

[a]For 4 patients, this was at 12 months, and for the other 2 patients, this was at 6 months, as they had not yet reached 12 months since MRgFUS capsulotomy.[72]

CGI Score

One study[79] also measured OCD symptoms using the CGI scale, a common clinical research tool administered by an experienced clinician to quantify and track a patient's psychiatric illness.[80] The CGI scale consists of 2 items: severity (CGI–S) and improvement (CGI–I). CGI–S reflects an assessment of psychopathology over the past week (rated from 1 to 7, with higher scores reflecting greater severity), whereas CGI–I reflects on improvements since a treatment was administered (rated from 1 to 7, with lower scores reflecting improvement and higher scores reflecting worsening).[80] The descriptions of each score for CGI–S and CGI–I are listed in the footnotes of Table 6. Each CGI item is a single question, assessed at baseline and subsequent visits. Given that CGI–I is assessed relative to pretreatment, there is no baseline score.

CGI was assessed at baseline, 1 week, and 1, 3, 6, 12, and 24 months after MRgFUS capsulotomy. The mean baseline CGI–S score was about 6 (i.e., severely ill). As shown in Table 6, CGI–I scores showed a statistically significant decrease over 24 months of follow-up ($P < .001$), with mean scores of approximately 2 (i.e., much improved) at the last follow-up.[79] Similarly, a statistically significant reduction was seen for CGI–S scores after MRgFUS capsulotomy, with a mean score at 24 months of approximately 4 (i.e., moderately ill; $P = .001$).[79]

The GRADE quality of the evidence was rated as Very low, given limitations related to imprecision (Appendix 3, Table A3).

Table 6: CGI Scores Over 24-Month Follow-Up After MRgFUS Capsulotomy

	CGI scores, mean (SD)							
Scale	Baseline	1 wk	1 mo	3 mo	6 mo	12 mo	24 mo	*P* value[a]
CGI–S[b]	6.1 (0.2)	5.6 (0.2)	5.4 (0.3)	4.5 (0.2)	4.4 (0.2)	4.0 (0.2)	3.9 (0.3)	.001
CGI–I[c]	—	3.4 (0.2)	3.2 (0.3)	2.7 (0.2)	2.5 (0.2)	2.0 (0.3)	2.1 (0.3)	<.001

Abbreviations: CGI, Clinical Global Impression; CGI–I, Clinical Global Impression – Improvement; CGI–S, Clinical Global Impression – Severity; MRgFUS, magnetic resonance-guided focused ultrasound; SD, standard deviation.

[a]Analyzed using a linear mixed model for repeated measures across the 24-month follow-up period.

[b]Scores reflect the severity of mental illness the patient is experiencing at a given time (1, normal, not at all ill; 2, borderline; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; 7, among the most extremely ill patients).[80]

[c]Scores reflect the patient's condition relative to before the initiation of treatment (1, very much improved since treatment initiation; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; 7, very much worse).[80]

Source: Kim et al.[79]

Treatment Response

More than half of the participants in the studies experienced complete or partial treatment response (Table 7); however, the definition of response differed between studies. Davidson et al[72] defined treatment response considering the Y–BOCS score, whereas Kim et al[79] considered both Y–BOCS and CGI scores to define response.

In the study by Davidson et al,[72] 4 patients (66.7%) met the criteria for complete response (≥35% reduction in Y−BOCS score) at last follow-up. The remaining 2 patients did not meet the criteria for partial response. In aggregate, the mean reduction at last follow-up (−33.3%; Table 5) did not meet the predefined criteria for complete response but qualified as partial response (>25% to <35% reduction in Y−BOCS score).

In the study by Kim et al,[79] patients' standard Y–BOCS score reductions and CGI scores were both considered in the categorization of responders (≥35% reduction in Y–BOCS score, and CGI–I score of 1 or 2), partial responders (25% to 35% reduction in Y–BOCS score, and CGI–I score of ≥3), or remission (Y–BOCS score of ≤12, and CGI–S score of 1 or 2). Nearly 55% (n = 6) of those who underwent MRgFUS capsulotomy were considered responders at the 12-month follow-up, and about 27% (n = 3) were partial responders. At 24 months after the procedure, 1 person (9.1%) was in remission, while the proportion of responders remained the same at nearly 55% (n = 6) and about 18% of participants (n = 2) were partial responders.

The GRADE quality of the evidence was rated as Very low, given limitations related to imprecision (Appendix 3, Table A3).

Table 7: Treatment Response After MRgFUS Capsulotomy

Author, year	Time point	Responders, % (n)	Partial responders, % (n)	Remission, % (n)	Nonresponders, % (n)
Davidson et al, 2020[72]	Last follow-up[a]	66.7 (4)	NR	NR	33.3 (2)
Kim et al, 2018[79]	12 mo	54.5 (6)[b]	27.3 (3)[c]	—	18.2 (2)
	24 mo	54.5 (6)	18.2 (2)	9.1 (1)[d]	18.2 (2)

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

[a]For 4 patients, this was 12 at months, and for the other 2 patients, this was at 6 months, as they had not yet reached 12 months since MRgFUS capsulotomy.[72]

[b]Defined as ≥35% reduction from baseline Y–BOCS score and much or very much improved on CGI–I (i.e., rating of 1 or 2).[79]

[c]Defined as 25% to 35% reduction from baseline Y–BOCS score and minimally improved on CGI–I (i.e., rating ≥ 3).[79]

[d]Defined as Y–BOCS score ≤ 12 and normal or borderline mentally ill on CGI–S (i.e., rating of 1 or 2).[79]

Adverse Events

Both studies commented on the absence of serious adverse events or persistent physical, neurological, or psychological complications.[72,79] Davidson et al[72] reported that no serious treatment-related adverse events occurred during the study, and that there were no suicide attempts during follow-up.

Kim et al[79] reported that none of the adverse events observed in previously published studies on RFA capsulotomy – fatigue, urinary incontinence, seizures, and behavioural changes (e.g., hypomania, personality changes, emotional blunting, indifference, or carelessness) – occurred in any patient during the 24 months of follow-up after MRgFUS capsulotomy. They also commented that no mania or hypomania; impulsivity, disinhibition, or executive dysfunction; or alcohol consumption was reported by patients or observed by their caregivers and psychiatrists over the study period.

The procedure was well tolerated by patients, with nearly two-thirds experiencing some transient adverse effect. The presence of physical or neurological adverse effects during the procedure was assessed before and after each sonication (range 23 to 26 sonications, lasting 10 to 31 seconds each) by both a neurosurgeon (i.e., lateralizing symptoms and signs) and a psychiatrist (i.e., mood changes, decreases in cognition).[78]

Nonserious adverse effects occurred in 4 of 6 patients with OCD (66.6%) who underwent MRgFUS capsulotomy in the study by Davidson et al.[72] The most common nonserious adverse effects were swelling (n = 2, 33.3%), redness or pain at the stereotactic head frame pin site (n = 2, 33.3%), and mild headaches (n = 3, 50%). These effects lasted from less than 24 hours to 5 days, and no intervention was reportedly needed to resolve them[72] (Table 8).

Kim et al[79] similarly reported transient nonserious adverse effects that resolved spontaneously, at completion of the procedure, or with a single dose of medication. The most common nonserious adverse effects were headache (n = 7, 63.6%), vestibular symptoms (e.g., nausea or vomiting; n = 5, 45.5%), anxiety (n = 3, 27.3%), stomach upset (n = 2, 18.2%), and transient warm sensation in the brain (n = 1, 9.1%).[79] The study also reported that there were no statistically significant changes in body weight during the 24-month follow-up period.

The GRADE quality of the evidence was rated as Very low, given limitations related to imprecision (Appendix 3, Table A3).

Table 8: Nonserious Adverse Events During and After MRgFUS Capsulotomy

Adverse event reported	n (%)	Details
Davidson et al, 2020[72]		
Headache	3 (50%)	Duration <24 h to 5 d and resolved without intervention
Pin-site swelling	2 (33.3%)	
Pin-site erythema	2 (33.3%)	
Kim et al, 2018[79]		
Headache – short, periodic, mild during procedure at high-temperature sonications	7 (63.6%)	Resolved spontaneously or after 1 dose of analgesic medication
Nausea, vomiting, dizziness during procedure	5 (45.5%)	Resolved at end of procedure or after 1 dose of antiemetic medication
Increased anxiety	3 (27.3%)	Resolved after 1 dose of benzodiazepine
Stomach upset	2 (18.2%)	Resolved with 1 dose of H_2 blocker medication
Transient warm sensation in brain during high sonications	1 (9.1%)	None reported

Abbreviations: H_2, histamine type 2 receptor; MRgFUS, magnetic resonance-guided focused ultrasound.

Neurocognitive Changes

Both studies administered a series of neuropsychological tests during the study.

In the Canadian case series,[75] 5 of 6 patients with OCD underwent baseline and postoperative neuropsychological assessment including verbal learning, visuospatial memory, executive function, frontal systems behaviour, and symbol-digit testing. A series of tests assessing intellectual function, executive function, episodic memory, and processing speed was administered at baseline and at 6 and 12 months after the procedure. The Wechsler Test of Adult Reading (WTAR) was measured only once and determined that baseline intellectual functioning was average to high-average. Tests administered after MRgFUS capsulotomy included the California Verbal Learning Test, second edition (CVLT-II; comprising 4 scores: total recall, delayed free recall, delayed cued recall, and delayed recognition discrimination); the Brief Visuospatial Memory Test – Revised (BVMT-R; immediate and delayed recall scales); the Symbol Digit Modalities Test (SDMT); the Frontal Systems Behavior Scale (FrSBe; self-report version, including total, apathy, disinhibition, and dysexecutive scores, with lower scores representing fewer behavioural symptoms); the Delis–Kaplan Executive Function System (D-KEFS) sorting test (correct sorts and description scores); and the Iowa Gambling Task (IGT). To minimize practise effects on the repeated tests, different versions (alternate forms) of the CVLT-II, D-KEFS sorting test, and BVMT-R were used at measurement time points; therefore, scores were standardized using published normative data for analysis.

In their statistical analysis, Davidson et al[75] combined the results of 5 patients who had OCD with the results of 5 patients who had treatment-refractory major depressive disorder to determine the change in test scores after MRgFUS capsulotomy from baseline. A change of ≥2 standard deviations (SD) on each neuropsychological test was considered clinically meaningful. Davidson et al[75] report that there were no negative effects of MRgFUS capsulotomy on cognitive or behavioural function, and potentially some modest improvements in apathy and executive function for patients with OCD and patients with major depressive disorder. Among the 5 patients with OCD, 1 exhibited improved performance of ≥2 SD on at least 1 score at 6 months, and 4 patients showed improvement of ≥2 SD on at least 1 measure at 12 months. None of the patients with OCD experienced a clinically meaningful decline (i.e., ≥2 SD from

baseline) on any neuropsychological test score at the 6- or 12-month follow-up after MRgFUS capsulotomy. As there were no statistical analyses of the neuropsychological test results for only the patients with OCD, we calculated the mean scores over the study period for the patients with OCD from available data in the report by Davidson et al[75] to provide a descriptive overview (Appendix 5, Table A4).

In the South Korean study,[79] an analogous series of neuropsychological tests was conducted at baseline and at 6, 12, and 24 months after MRgFUS capsulotomy (Table 9). The tests assessed intellectual function (Wechsler Adult Intelligence Scale, Korean version [K-WAIS]), memory (memory quotients of the Rey-Kim Memory Test), executive function (Controlled Oral Word Association Test [COWAT] and Korean Colour Word Stroop Test [Stroop]), and attention (Digit Span test). All 11 study participants completed the tests at baseline and at the 6-month follow-up. However, only 8 participants completed the neuropsychological tests at 12 months, and 10 participants completed them at the 24-month follow-up. Changes in neuropsychological function over the study period were statistically analyzed using a linear mixed model for repeated measures, as well as with post hoc analyses of change from baseline for each variable at each time point, with Bonferroni correction.

No statistically significant changes were observed in executive function, intellectual function, or attention after MRgFUS capsulotomy.[79] Memory quotient scores improved over 24 months of follow-up (statistically significant, $P < .001$); however, practise effects cannot be ruled out as a potential contributor to this finding. There were no statistically significant changes in the other neuropsychological tests assessed after the procedure (i.e., K-WAIS, COWAT, Stroop, and Digit Span; Table 9).

The GRADE quality of the evidence was rated as Very low, given limitations related to risk of bias and imprecision (Appendix 3, Table A3).

Table 9: Neuropsychological Function Before and After MRgFUS Capsulotomy

Test	Function(s) measured	Baseline, mean (SD) (n = 11)	6 mo, mean (SD) (n = 11)	12 mo, mean (SD) (n = 8)	24 mo, mean (SD) (n = 10)	*P* value
Wechsler Adult Intelligence Scale, Korean version (K-WAIS)	Cognitive ability	90.9 (19.3)	93.5 (19.7)	95.9 (20.7)	95.5 (14.0)	>.05
Memory quotients of the Rey-Kim Memory Test	Memory	94.4 (13.9)	103.3 (13.3)	110.3 (13.7)	110.1 (14.8)	<.001
Controlled Oral Word Association Test (COWAT)	Verbal fluency – semantic	19.5 (6.4)	18.3 (5.8)	18.3 (6.6)	17.4 (3.9)	>.05
	Verbal fluency – phonemic	35.5 (15.0)	38.2 (20.6)	41.1 (14.3)	36.6 (7.0)	>.05
Korean Colour Word Stoop Test	Cognitive processing	1.25 (0.32)	1.30 (0.48)	1.22 (0.45)	1.16 (0.28)	>.05
Digit Span test	Memory	10.2 (2.3)	10.1 (2.5)	11.3 (2.8)	11.4 (2.2)	>.05

Abbreviations: OCD, obsessive–compulsive disorder; MRgFUS, magnetic resonance-guided focused ultrasound; SD, standard deviation.
Source: Kim et al.[79]

Technical Failure

The information available on technical failure pertained to the inability to complete the procedure (i.e., create a therapeutic lesion), as opposed to issues with the technology (e.g., device malfunction). MRgFUS capsulotomy could not be completed in 2 of the 8 people with treatment-refractory OCD (25%) enrolled in the Canadian clinical trial (see Figure 2 in the report by Davidson et al[72]). This was reportedly due to an inability to sufficiently heat the target area of the brain because of individual skull factors (e.g., skull-density ratio) hindering the transmission of ultrasound. Given that the procedure could not be completed in these patients, there are no outcome data or information for these 2 participants.

A preliminary report[78] from the South Korean clinical trial on the first 6 patients with OCD (recruited between March 2012 and August 2013) noted 1 technical failure due to insufficient temperature rise related to skull factors (e.g., density, thickness). This 1 technical failure for OCD was reported alongside 3 technical failures for essential tremor, where the mean skull-density ratio of this group of cases combined was 0.3 and maximal temperature was less than 45°C. The final publication of the entire case series[79] reported and displayed in their patient flow that all people enrolled and eligible completed the procedure; therefore, it is unclear when the technical failure for OCD reported in the earlier publication occurred and how it was counted.

The GRADE quality of the evidence was rated as Very low, given limitations related to risk of bias and imprecision (Appendix 3, Table A3).

Follow-Up Interventions and Re-treatment

No subsequent interventions or re-treatment after MRgFUS capsulotomy were reported for patients with OCD in either study.[72,79] The GRADE quality of the evidence was rated as Very low, given limitations related to imprecision (Appendix 3, Table A3).

Quality of Life and Functionality

Quality of Life Enjoyment and Satisfaction

Davidson et al[72] assessed quality of life preoperatively and postoperatively via the Quality of Life Enjoyment and Satisfaction Questionnaire as a secondary outcome. This self-reported tool captures a person's degree of enjoyment and satisfaction across various aspects of daily functioning (e.g., leisure time activities, physical health, social relationships, subjective feelings, general activities).[81] Higher scores indicate greater enjoyment and satisfaction.[81] One participant treated on humanitarian or compassionate grounds (i.e., outside of the clinical trial eligibility) did not have a baseline measurement, so complete data are available for only 5 of 6 participants with OCD (83.3%). There was no statistical testing for the before-and-after comparison; however, quality-of-life scores after the procedure were numerically higher than at baseline (Table 10). The GRADE quality of the evidence was rated as Very low, given limitations related to imprecision (Appendix 3, Table A3).

Table 10: Quality of Life Before and After MRgFUS Capsulotomy

	Baseline Q-LES-Q		Follow-up Q-LES-Q	
Author, year	**Mean (SD)**	**n**	**Mean (SD)**	**n**
Davidson et al, 2020[72]	32.2 (11.6)	5[a]	41.8 (15.1)	5[a]

Abbreviations: MRgFUS, magnetic resonance-guided focused ultrasound; Q-LES-Q, Quality of Life Enjoyment and Satisfaction Questionnaire; SD, standard deviation.

[a]One participant was treated on humanitarian or compassionate grounds (i.e., outside of the clinical trial) and did not have a baseline Q-LES-Q measurement. This patient's score after MRgFUS capsulotomy was 61.[72]

Psychosocial and Occupational Functioning

Kim et al[79] assessed psychosocial and occupational functioning using the Global Assessment of Functioning (GAF) scale. The GAF scale is a non-disease-specific clinician assessment of the severity of mental illness symptoms and their impact on the psychological, social, and occupational functioning of a patient.[82,83] The score ranges from 0 to 100, with higher scores indicating better functioning.[82,83] All study participants had psychosocial dysfunction (i.e., GAF of ≤50 at the start of the study; mean, 35.8). GAF was administered at baseline and at 3, 6, 12, and 24 months after MRgFUS capsulotomy and was documented to have statistically significant improvement across the study period (Table 11). Statistically significant improvements from baseline were seen as early as 3 months after the procedure ($P < .001$, with Bonferroni correction).[79] The GRADE quality of the evidence was rated as Very low, given limitations related to imprecision (Appendix 3, Table A3).

Table 11: GAF Scores Over 24-Month Follow-Up After MRgFUS Capsulotomy

	GAF score, mean (SD)					
Author, year	**Baseline**	**3 mo**	**6 mo**	**12 mo**	**24 mo**	***P* value[a]**
Kim et al, 2018[79]	35.8 (4.98)	44.3 (3.6)	48.0 (7.1)	53.9 (10.8)	56.0 (10.3)	<.001

Abbreviations: GAF, Global Assessment of Functioning; MRgFUS, magnetic resonance-guided focused ultrasound; SD, standard deviation.

[a]Linear mixed model for repeated measures to analyze change in scores across the 24-month follow-up period.

Ongoing Studies

We identified 1 future study in the US that will assess the effectiveness and safety of bilateral MRgFUS capsulotomy for treatment-refractory OCD.[84] The "Sonication-based OCD Neurosurgical Intervention Via Capsulotomy (SONIC)" study is planned to begin in June 2024 and involve 2 stages: first, a case series of people with severe, treatment-refractory OCD (planned recruitment, n = 10), and subsequently, people with moderate-to-severe, treatment-refractory OCD (planned recruitment, n = 56). In stage 1, participants with severe OCD will receive MRgFUS capsulotomy and be followed with best medical care for 12 months. The investigators will then submit an Investigational Device Exemption supplement to the US Food and Drug Administration (FDA) and, if approved, the second stage of the study will proceed. Stage 2 will involve a period of randomization for participants with moderate-to-severe OCD to MRgFUS capsulotomy or sham, with follow-up and crossover to MRgFUS capsulotomy for nonresponders assigned to the sham group. The study will use the Exablate Neuro MRgFUS system and technical protocol based on that used in the South Korean and Canadian studies included in this review. Data collection on primary outcomes is forecasted to be completed in June 2030, and study completion in 2032.

The research group of the included study by Davidson et al[72] is preparing a manuscript reporting on an additional 6 patients with severe, treatment-refractory OCD who received MRgFUS capsulotomy in their clinical trial. The manuscript will report outcomes for all 12 patients and with longer follow-up (C. Hamani, MD, PhD; B. Davidson, MD; and N. Lipsman, MD, PhD; email communication, December 7, 2023).

Discussion

Our systematic review identified 2 small case series that examined MRgFUS in 17 patients. Very low certainty evidence suggests that MRgFUS capsulotomy may lead to clinically meaningful improvement in OCD symptoms for people with severe, treatment-refractory OCD. The severity of OCD symptoms in the studies improved on average from extreme at baseline to moderate after MRgFUS capsulotomy. The beneficial effects materialized over the weeks and months following the procedure, and most but not all patients experienced partial or complete treatment response, despite variable definitions of treatment response between studies. In addition, though adverse effects during or immediately following the procedure were common, all were mild and transient. The studies did not document any issues with conscious sedation, serious or persistent adverse events, or declines in neurocognitive function after MRgFUS capsulotomy. Importantly, quality of life and functioning improved for patients.

It is difficult to contextualize the effects of MRgFUS within other neurosurgeries for OCD given the absence of comparative studies. The rate of treatment response observed after MRgFUS capsulotomy in our review was in a range similar to that reported in published studies of capsulotomy performed with RFA or Gamma Knife (i.e., approximately 50%–60%),[13,23,27] which represents a substantial change in the trajectory of a severe, treatment-refractory illness. Capsulotomy with MRgFUS is noninvasive and uses sound waves, thereby avoiding the risks of open surgery or ionizing radiation required by other capsulotomy techniques. The observed safety profile of MRgFUS capsulotomy differs from those of RFA and Gamma Knife capsulotomy, after which up to 5% and 20% of patients, respectively, can experience serious adverse events (e.g., infection, hemorrhage, brain cyst) or declines in neuropsychological function.[13,23,27,33] It has been posited that the favourable adverse-effect profile of MRgFUS capsulotomy may be partly attributed to the ability to create smaller, more precise lesions with MRgFUS technology.[75] It is not possible for all patients to undergo MRgFUS neurosurgery successfully. Treatment failure, due to the inability to sufficiently heat the target area and create a therapeutic lesion, is sometimes precluded by individual anatomical factors such as skull density and thickness. In capsulotomy, the target is deeper in the brain than the target of movement disorders (e.g., ventral intermediate nucleus), and heating efficacy at the target is decreased as a result of the skull heating during the procedure.[76] The limitations of focused ultrasound depth penetration are the reason that capsulotomy is the only ablative neurosurgery that can be done with current technology of MRgFUS, as it is not possible to reach deeper targets (e.g., for cingulotomy).[74] Treating clinicians must highlight the possibility of MRgFUS failure to patients when eliciting informed consent.[76]

The positive effects of MRgFUS capsulotomy appeared durable after the procedure for 6, 12, or 24 months, and no latent adverse events appeared in the studies. Side effects occurred peri-operatively (within days of the procedure) and improved quickly, whereas the beneficial effects accrued and sustained over time. No instances of re-treatment occurred, likely as bilateral lesions were successfully created for all study participants in whom MRgFUS was possible. Among the patients with treatment-refractory major depressive disorder reported by Davidson et al,[76] 1 case of re-treatment (i.e., second-side lesion creation) with MRgFUS was completed without adverse events and with some subsequent clinical improvement.

Though some patients in 1 study had changes in their medication after MRgFUS capsulotomy, this is not particularly relevant. OCD is a chronic condition and requires ongoing, comprehensive treatment, including ERP and/or pharmacotherapy. As with all neurosurgeries for treatment-refractory OCD, MRgFUS neurosurgery is not intended to be curative. Rather, neurosurgery may change brain response to medication or enable improved participation in – and, thereby, effectiveness of – ERP therapy.[85]

Equity Considerations

There was little information in the included studies about PROGRESS-Plus[62] characteristics, across which health inequities may exist. Therefore, we cannot comment on who was or was not represented in the available evidence. Improvements in both capacity and coordination of the spectrum treatment for OCD are required to facilitate equitable access for patients. Factors such as geography, variable or poor access to primary and tertiary mental health care, and the stigmatization of mental illness and its surgical treatments may contribute to inequities in access. Neurosurgery for OCD, including MRgFUS neurosurgery, requires a referral from a physician, typically a treating psychiatrist. At present, there is no clear treatment or referral pathway for patients with OCD in Ontario to facilitate access to psychiatrists or neurosurgical consultation for those with severe, treatment-refractory disease.

Strengths and Limitations

To our knowledge, this is the first systematic review of the effect of MRgFUS neurosurgery for severe, treatment-refractory OCD. The body of evidence consists of case series; therefore, we cannot compare the effectiveness or safety with that of other neurosurgeries. Case series studies lack statistical power and are at increased risk of bias given that there is no control group.[67] This is unsurprising in this field of clinical research, as despite decades of neurosurgery for severe, treatment-refractory OCD, there remain no studies comparing DBS with ablative neurosurgery.[19] Several reasons may contribute to this, including the higher cost of DBS, preference by providers and patients for reversible treatment, and that DBS and ablative neurosurgery may not both be suitable for the same population.[32] Clinical trials of neurosurgery for OCD are challenged by ethical considerations, the difficulty in recruiting sufficient numbers of participants (partly due to low numbers of referrals for surgery), and a latency of years to observe outcomes.[32] The forthcoming data on MRgFUS neurosurgery for OCD that we are aware of (see Ongoing Studies) does not compare MRgFUS with other surgical methods for capsulotomy.

We aspired to meta-analyze the data on treatment response; however, this was not appropriate due to differing outcome definitions. In addition, the small sample sizes and low number of studies posed challenges for meaningful quantitative synthesis.[86] As a strength, the 2 included case series were preplanned, prospective, and applied clear inclusion criteria, follow-up, and measurement of the condition and outcomes. It was unclear whether the series represent consecutive and complete inclusion of cases at each centre, which could contribute to the reliability of a case series.[67] There is considerable uncertainty about the effect estimates due to limitations in the quality of the body of evidence (Appendix 3, Table A3). However, MRgFUS neurosurgery is reserved for people with OCD who are extremely disabled by their condition and have not responded to all other treatment options. OCD symptoms tend to remain stable over time,[87,88] and remission is rare over the long term.[89] Untreated, severe OCD is associated with an elevated risk of suicide,[8] reduced quality of life,[90] and caregiver burnout[91] and invariably results in chronic disability.[11]

Conclusions

There is considerable uncertainty; however, the evidence suggests that MRgFUS capsulotomy for severe, treatment-refractory OCD:

- May improve OCD symptoms (GRADE: Very low) and result in treatment response (GRADE: Very low)
- May have a favourable safety profile (GRADE: Very low); no occurrences of serious or persistent adverse events were reported
- May have little to no effect on neurocognitive function (GRADE: Very low)
- May have a technical failure rate of up to 25% (GRADE: Very low)
- May improve quality of life (GRADE: Very low)
- May improve patient functioning (GRADE: Very low)
- May not require re-treatment or follow-up interventions; however, the evidence is very uncertain, as no occurrences were reported (GRADE: Very low)

Economic Evidence

Research Question

What is the cost-effectiveness of magnetic resonance-guided focused ultrasound (MRgFUS) neurosurgery compared with radiofrequency ablation (RFA), Gamma Knife radiosurgery, and deep brain stimulation (DBS) for the treatment of people with treatment-refractory obsessive–compulsive disorder (OCD)?

Methods

Economic Literature Search

We performed an economic literature search on August 14, 2023, to retrieve studies published from database inception until 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, Embase, and APA PsycInfo and monitored them until February 16, 2024. We also performed a targeted grey literature search following a standard list of websites developed internally, which includes the International HTA Database and the Tufts Cost-Effectiveness Analysis Registry. See Clinical Literature Search, above, for further details on methods used. See Appendix 2 for our literature search strategies, including all search terms.

Eligibility Criteria

Studies

Inclusion Criteria

- English-language full-text publications
- Cost–benefit analyses, cost-effectiveness analyses, cost–utility analyses, cost–consequence analyses, or cost analyses

Exclusion Criteria

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

Population

- Adults (≥18 years old) with severe, treatment-refractory OCD, as defined by the study

Interventions

- MRgFUS neurosurgery, with or without co-interventions (such as psychotherapy and/or pharmacotherapy)

Comparators

- RFA, with or without co-interventions (such as psychotherapy and/or pharmacotherapy)
- Gamma Knife radiosurgery, with or without co-interventions (such as psychotherapy and/or pharmacotherapy)
- DBS, with or without co-interventions (such as psychotherapy and/or pharmacotherapy)
- No comparator

Outcome Measures

- Costs
- Health outcomes (e.g., partial or complete response, change in Yale–Brown Obsessive–Compulsive Scale [Y–BOCS] score, quality-adjusted life-years [QALYs])
- Incremental costs
- Incremental effectiveness
- Incremental cost-effectiveness ratios (ICERs)

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Microsoft Excel[92] and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. The same reviewer then examined the full-text articles and selected studies eligible for inclusion.

Data Extraction

We extracted relevant data on study characteristics and outcomes to collect information about the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, analytic technique, perspective, time horizon, population, intervention[s], comparator[s])
- Outcomes (e.g., health outcomes, costs, ICERs)

We contacted study authors to provide clarification as needed.

Study Applicability and Limitations

We determined the usefulness of each identified study 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 to inform the development of NICE's clinical guidelines.[93] We modified the wording of the questions to remove references to guidelines and to make it specific to Ontario. Next, we separated the checklist into 2 sections. In the first section, we assessed the applicability of each study to the research question (directly, partially, or not applicable). In the second section, we assessed the limitations (minor, potentially serious, or very serious) of the studies that we found to be applicable.

Results

Economic Literature Search

The economic literature search yielded 17 citations, including grey literature results and after removing duplicates, published from database inception until August 14, 2023. We identified no additional eligible studies from other sources, including database alerts (monitored until February 16, 2024). In total, we identified 1 study (a threshold analysis) that met our inclusion criteria. Figure 2 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the economic literature search.

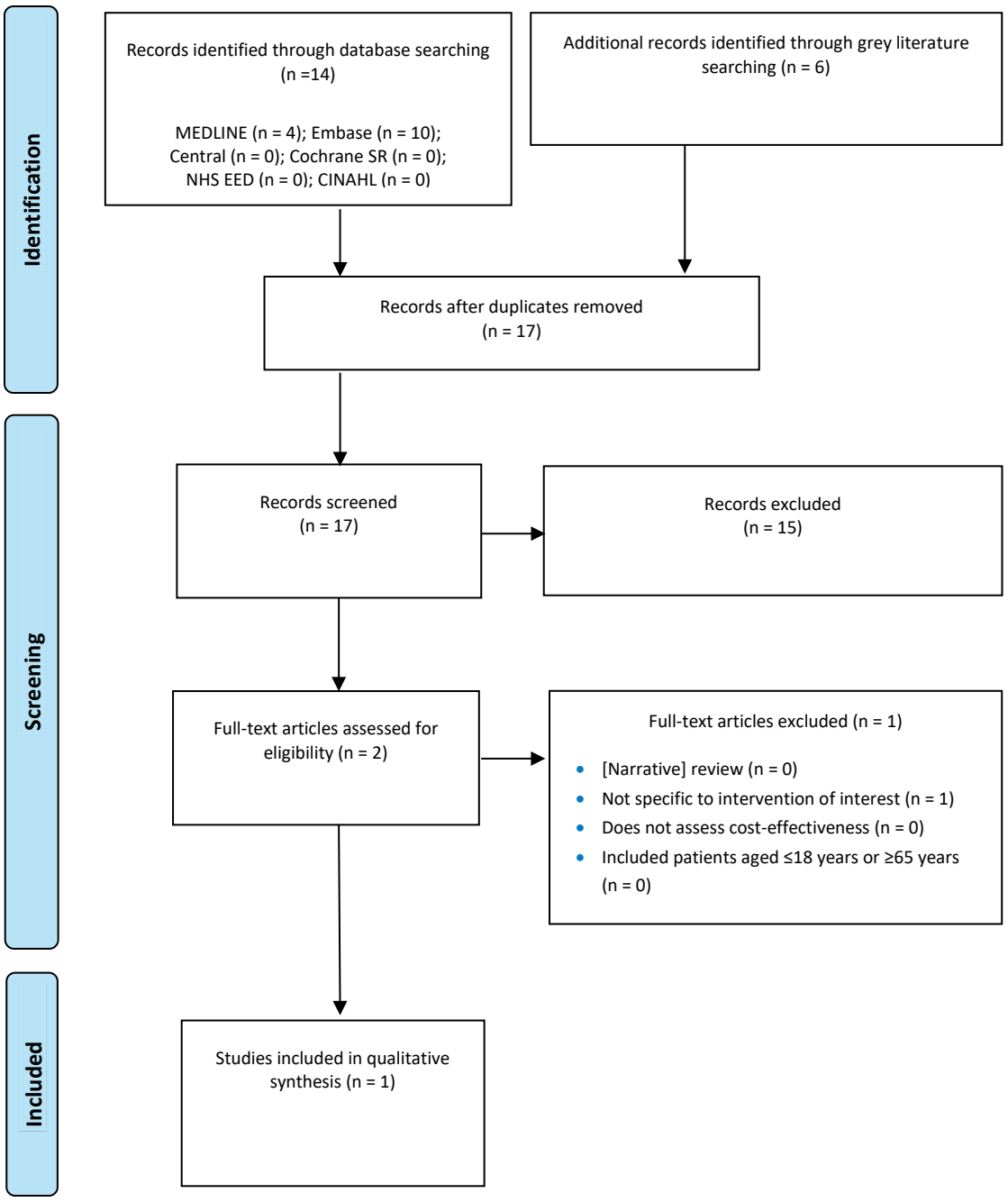

Figure 2: PRISMA Flow Diagram – Economic Systematic Review

PRISMA flow diagram showing the economic systematic review. The economic literature search yielded 14 citations published between database inception and August 14, 2023. We included 6 additional studies from other sources. After removing duplicates, we screened the abstracts of the 17 identified studies and excluded 15. We assessed the full text of 2 articles and excluded a further 1. In the end, we included 1 article in the qualitative synthesis.

Abbreviations: CINAHL, Cumulative Index to Nursing and Allied Health Literature; Cochrane SR, the Cochrane Database of Systematic Reviews; NHS EED, National Health Service Economic Evaluation Database; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Source: Adapted from Page et al.[61]

Overview of Included Economic Studies

We identified 1 economic study investigating the cost-effectiveness of MRgFUS neurosurgery for the treatment of patients with OCD.[94] Kumar et al[94] investigated the cost-effectiveness of MRgFUS neurosurgery compared with radiofrequency capsulotomy, a type of RFA, for people with treatment-refractory OCD. A summary of the included study is provided in Table 12.

Kumar et al[94] conducted a threshold analysis to estimate the necessary cost and clinical parameters for MRgFUS to conclude that MRgFUS neurosurgery is cost-effective compared with RFA. The authors stated that this decision was made due to the limited clinical data evaluating MRgFUS neurosurgery for OCD, as only 1 case series of 4 patients published by Jung et al[78] was available at the time of their analysis.

The analysis used a decision tree over a 1-year time horizon from a US societal perspective.[94] Effectiveness was defined as a reduction in Y–BOCS score. The effectiveness of RFA was derived from an unpublished meta-regression of observational data in which change in Y–BOCS score was converted to mean improvement in utility. The costs for RFA and MRgFUS neurosurgery were derived from Medicare reimbursement rates.

The study estimated the 1-year cost of RFA to be $24,099 USD with 0.212 QALYs per patient.[94] Rather than reporting a single threshold value for the cost and clinical parameters of MRgFUS neurosurgery, a 3-way sensitivity analysis was graphically reported for utility of MRgFUS ranging from 0 to 0.5 QALYs, cost from $10,000 USD to $25,000 USD, and 10%, 20%, or 30% probability of complications. For most combinations of values of the variables identified, MRgFUS neurosurgery was cost-effective, and the authors concluded that MRgFUS neurosurgery was cost-effective under a wide range of values. However, there was no justification for the range of values used in the sensitivity analysis and a willingness-to-pay threshold was not provided.

Table 12: Characteristics of Studies Included in the Economic Systematic Review

Author, year, country, intervention, comparator	Analysis				Study population	Results		
	Technique	Design (model)	Approach or perspective	Time horizon (discount rate)		Health outcomes	Costs	Cost-effectiveness
Kumar et al, 2019,[94] US	Threshold analysis	Decision tree	Societal	1 y (N/A)	Patients with treatment-refractory OCD considered suitable candidates for surgery	—	Currency, cost year: USD, 2017	ICER not reported; study concluded that MRgFUS neurosurgery was cost-effective under a range of possible values, and results were most sensitive to cost, effectiveness, and complication rate of MRgFUS neurosurgery. PSA was not reported.
I: MRgFUS neurosurgery	—	—	—	—		NR	NR	
C: RFA	—	—	—	—		0.212 QALYs	$24,099 USD	

Abbreviations: C, comparator; I, intervention; ICER, incremental cost-effectiveness ratio; MRgFUS, magnetic resonance-guided focused ultrasound; N/A, not applicable; NR, not reported; OCD, obsessive–compulsive disorder; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; RFA, radiofrequency ablation.

Applicability of the Included Studies

Appendix 6, Table A5 provides the results of the quality appraisal checklist for economic evaluations applied to the included studies. One study[94] was included and was deemed not applicable to our research question. Although the study included the population, intervention, and comparator of interest, it is an early cost-effectiveness analysis based on theoretical data inputs and assumptions, as there was no clinical study comparing MRgFUS neurosurgery with RFA. The authors conducted a threshold analysis to determine when MRgFUS neurosurgery would be considered cost-effective compared with RFA.

There were no studies applicable to our research question, so no methodological quality assessment was applied.

Discussion

Kumar et al[94] conducted a threshold analysis to determine the cost and clinical parameters of MRgFUS neurosurgery required for it to be cost-effective compared with RFA. The authors acknowledged the lack of data on MRgFUS neurosurgery and did not provide any sources or justification for MRgFUS neurosurgery clinical input data.

Strengths and Limitations

We conducted a thorough review of the economic literature to examine the cost-effectiveness of MRgFUS neurosurgery for severe, treatment-refractory OCD. We were limited in our conclusions about the cost-effectiveness of MRgFUS neurosurgery by the paucity of evidence identified.

Conclusions

We identified 1 study conducted by Kumar et al[94] that we deemed not applicable to our research question. Kumar et al[94] conducted a threshold analysis because of limited clinical data on MRgFUS neurosurgery. They concluded that MRgFUS neurosurgery could be cost-effective for a range of input values but acknowledged that their model is not a substitute for randomized controlled trials directly comparing strategies and that data on long-term efficacy and complications could impact cost-effectiveness findings.

Primary Economic Evaluation

Although 2 trials examining magnetic resonance-guided focused ultrasound (MRgFUS) neurosurgery in patients with severe, treatment-refractory obsessive–compulsive disorder (OCD) have been completed and published, the studies are limited by small sample sizes and were conducted without comparator arms (see Strengths and Limitations in Clinical Evidence).[47,74,79,95] Due to the lack of comparative clinical evidence, we did not conduct a primary economic evaluation.

Budget Impact Analysis

Research Question

What is the potential 5-year budget impact for the Ontario Ministry of Health of publicly funding magnetic resonance-guided focused ultrasound (MRgFUS) neurosurgery for people with treatment-refractory obsessive–compulsive disorder (OCD)?

Methods

Analytic Framework

We estimated the budget impact of publicly funding MRgFUS neurosurgery using the cost difference between 2 scenarios: (1) current clinical practice without public funding for MRgFUS neurosurgery (the current scenario) and (2) anticipated clinical practice with public funding for MRgFUS neurosurgery (the new scenario). Figure 3 presents the budget impact model schematic.

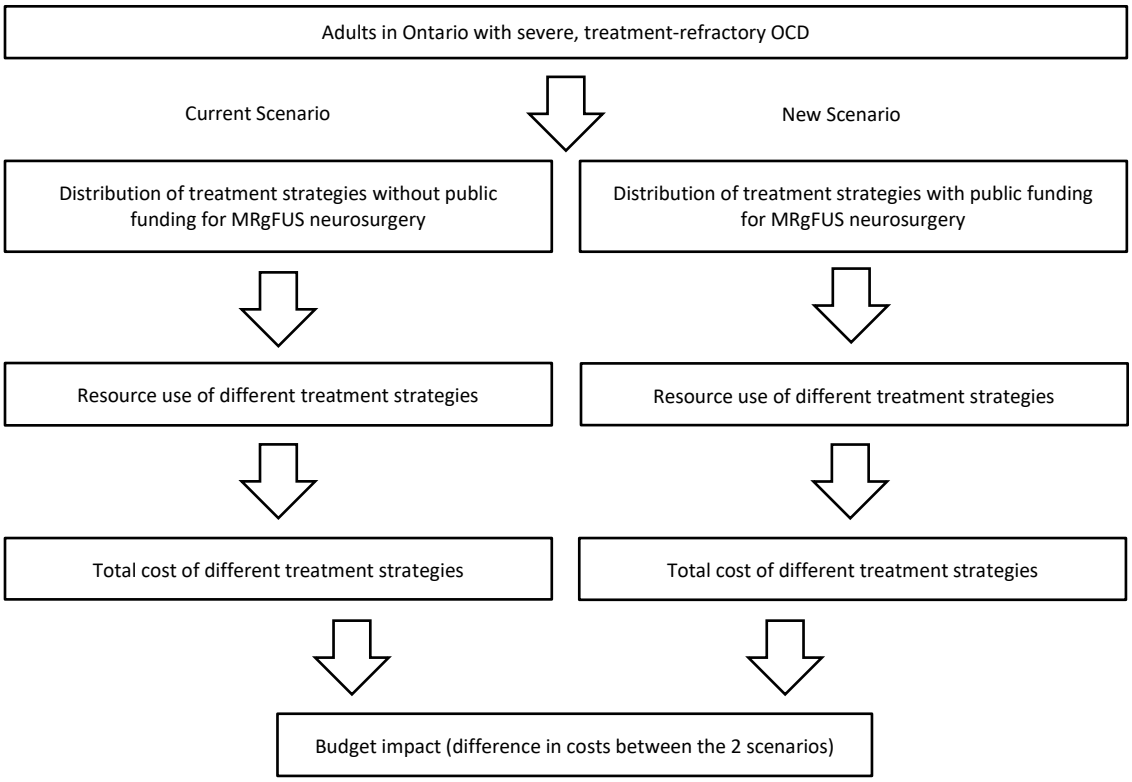

Figure 3: Schematic Model of Budget Impact

Flow chart describing the model for the budget impact analysis. Based on the size of the population of interest, we created 2 scenarios: the current scenario, which would explore the distribution of treatment strategies, resource use, and total costs without public funding for MRgFUS neurosurgery; and the new scenario, which would explore the distribution of treatment strategies, resource use, and total costs with public funding for MRgFUS neurosurgery. The budget impact would represent the difference in costs between the 2 scenarios.

Key Assumptions

We made the following assumptions:

- Interventions were performed in hospitals with existing infrastructure (e.g., magnetic resonance imaging [MRI] suite); therefore, capital and fixed costs for equipment were not included.
- Any adjunct pharmacotherapy remained constant before and after treatment.
- Adverse events occurred within the first year of treatment; thus, costs were incurred in the same year as treatment.
- Only costs of serious adverse events resulting in hospitalization were included.
- Deep brain stimulation (DBS) for OCD is available only through research and is not publicly funded; therefore, it incurred no costs from the Ministry of Health perspective.

Population of Interest

The size of the population of interest (people in Ontario with severe, treatment-refractory OCD) was estimated based on published epidemiological data and expert opinion.

We used population projections from the Ontario Ministry of Finance to estimate the adult population (≥18 years old) in Ontario for 2024 to 2028.[96]

We applied the lifetime prevalence of OCD among people in Canada estimated from the 2012 Canadian Community Health Survey – Mental Health, (0.93%; 95% confidence interval, 0.75%–1.11%) to estimate the number of people in Ontario with OCD.[7] We estimated the distribution of OCD severity based on data from an epidemiological study in the US that measured severity of OCD using the Yale–Brown Obsessive–Compulsive Scale (Y–BOCS).[6] Nearly one-third (30.7%) of people with OCD were classified as having severe OCD (defined in the study as Y–BOCS score > 30). We applied this estimate to determine the number of eligible patients based on severity. Treatment rates for OCD were low; the same US study found that about 31% of people with severe OCD reported receiving OCD-specific treatment.[6]

Ontario Health's quality standard for OCD recommends a stepped-care approach beginning with the least intensive, efficacious treatment.[97] Primary treatment includes pharmacotherapy and psychotherapy.[2] However, for some people with OCD, primary treatment is insufficient and their OCD is treatment-refractory, meaning that there is insufficient response to or disabling side effects with at least first- and second-line therapy including at least 1 trial with adjuvant antipsychotic medication and at least 1 complete trial of cognitive behavioural therapy (CBT).[30] In the literature, estimates of the percentage of people with OCD who have treatment-refractory OCD vary, with one source reporting 30% to 40%.[14]

Insightec Ltd (Haifa, Israel), currently the only manufacturer of MRgFUS neurosurgery equipment, notes that people exhibiting behaviours consistent with substance abuse are contraindicated for the MRgFUS neurosurgical procedure.[98] Therefore, we removed approximately 11% (95% confidence interval, 5.35%–15.93%) of people with OCD from our population of interest, as this represents the percentage of people with OCD who also met the criteria for substance abuse or dependence in the last 12 months.[7]

People with severe, treatment-refractory OCD are potential candidates for MRgFUS neurosurgery; however, access to mental health care is limited. In the Canadian 2022 Mental Health and Access to Care Survey, about 49% of people who met diagnostic criteria for a mood, anxiety, or substance use disorder in the previous 12 months reported talking to any health professional about their mental health in the past year, and that percentage decreased to about 13% when asked about psychiatrists specifically.[99] An expert on OCD estimated that only about 50% of people have access to secondary or tertiary OCD-specialized psychiatrists (P. M. A. Richter, MD, email communication, October 9, 2023). Potential candidates for MRgFUS neurosurgery are screened by 2 psychiatrists who must independently conclude that the patient is a candidate for MRgFUS neurosurgery before a surgical referral is made. Criteria for screening may include checking for medical comorbidities, treatment history, duration of illness, and functional impairment. A clinical expert estimated that one-third of people referred for MRgFUS neurosurgery are medically and psychiatrically eligible for surgery (N. Lipsman, MD, PhD, email communication, December 14, 2023). In one site's experience with offering MRgFUS neurosurgery, 85% of people who are suitable candidates for surgery accepted the treatment (N. Lipsman, MD, PhD, email communication, December 14, 2023).

Once a patient is deemed to be a candidate for MRgFUS neurosurgery, there are additional criteria to ensure that the procedure will be successful, including a minimum skull-density ratio to ensure adequate heating to create a lesion. Boutet et al[100] reported skull-density ratios of patients with movement disorders who were candidates for MRgFUS thalamotomy, a type of ablative neurosurgery that targets a different location in the brain than capsulotomy. They found that a skull-density ratio of ≥0.4 was optimal and reported that 21 out of 136 patients (15%) failed to meet that criterion.[100] Although Davidson et al[74] suggest that MRgFUS capsulotomy may require a higher skull-density ratio cut-off of ≥0.45 due to the necessity of reaching a deeper brain structure, the proportion of patients who met this cut-off was not reported. In our reference case, we used the percentage of patients with a skull density ratio of ≥0.4 (85%) from the study by Boutet et al.[100]

Table 13 summarizes the process of estimating our population of interest: the number of people in Ontario with severe, treatment-refractory OCD who are candidates for MRgFUS neurosurgery.

Table 13: Process of Estimating the Population of Interest

Variable	Year 1 (2024)	Year 2 (2025)	Year 3 (2026)	Year 4 (2027)	Year 5 (2028)
Ontario population ≥ 18 years old[a]	12.8 million	13.0 million	13.3 million	13.5 million	13.7 million
People with OCD (0.93%)[7]	118,721	121,314	123,435	125,167	127,006
Y–BOCS severity score > 30 (30.7%)[6]	36,447	37,243	37,895	38,426	38,991
Treatment-seeking (30.9%)[6]	11,262	11,508	11,709	11,874	12,048
Treatment-refractory (35%)[14]	3,942	4,028	4,098	4,156	4,217
Without comorbid substance use disorder (89%)[7]	3,508	3,585	3,647	3,699	3,753
Access to secondary or tertiary OCD-specialized psychiatrist (50%)	1,754	1,792	1,824	1,849	1,876
Referred for MRgFUS neurosurgery (10%)	175	179	182	185	188
Medically and psychiatrically eligible for MRgFUS neurosurgery (33%)	58	59	60	61	62
Interest and consent to MRgFUS neurosurgery (85%)	49	50	51	52	53
Favourable skull density (85%)[100]	42	43	43	44	45

Note: Numbers may be inexact due to rounding.

Abbreviations: MRgFUS, magnetic resonance-guided focused ultrasound; OCD, obsessive–compulsive disorder; Y–BOCS, Yale–Brown Obsessive–Compulsive Scale.

[a]Data for ages 20 years and older were used, as data on ages 18 years and older were unavailable.

Current Intervention Mix

Canadian guidelines have scant recommendations on treatment options for people with OCD who are refractory to pharmacotherapy and psychotherapy.[2] Options for severe, treatment-refractory OCD include ablative neurosurgical options and DBS. There are 3 different methods that can be used for ablative neurosurgery: radiofrequency ablation (RFA), Gamma Knife radiosurgery, and MRgFUS neurosurgery (the intervention of interest).

There are only 2 sites in Ontario that have the equipment and expertise to offer any of these procedures. RFA and Gamma Knife radiosurgery are provided for patients with treatment-refractory OCD and are covered by the hospitals' global budgets. MRgFUS neurosurgery and DBS are being used off-label under humanitarian exemptions and are paid for by philanthropic or clinical trial funding (N. Lipsman, MD, PhD, email communication, October 9, 2023). Currently, there is only 1 site in Ontario that offers MRgFUS neurosurgery or Gamma Knife radiosurgery and 2 sites in Ontario that offer DBS or RFA for people with treatment-refractory OCD (IntelliHealth Ontario, August 4, 2023).

Although the population of interest was estimated at around 40 people per year, the number of people receiving these treatments in Ontario appears to be much lower, likely owing to a lack of awareness of treatment options or a lack of an established referral pathway for severe, treatment-refractory OCD (P. M. A. Richter, MD, email communication, October 9, 2023). A study conducted in Quebec that surveyed psychiatry residents and psychiatrists identified several barriers to referring patients for neurosurgery, including lack of knowledge on the technical aspects of the procedures, efficacy, potential side effects, eligibility criteria, availability, and referral process.[101] Other barriers included fear of irreversible consequences and patient or family resistance to the procedures.

We used the IntelliHealth Ontario portal to obtain the number of documented Gamma Knife radiosurgery and RFA procedures in the Canadian Institute for Health Information (CIHI) Discharge Abstract Database for Ontario from 2019 to 2022 (Table 14). Procedures were identified using the Canadian Classification of Health Interventions (CCI) codes as shown in Appendix 7, Table A6, with a main diagnosis of OCD identified by International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada (ICD-10-CA) codes (F42; see Appendix 7, Table A7). In Ontario, an average of about 4 patients with OCD received Gamma Knife radiosurgery (45%) or RFA (55%) annually from 2019 to 2022.

As DBS is not funded by the Ontario Ministry of Health and we are taking the Ministry of Health perspective for our analysis, we did not include treatment with DBS in our reference case. We conducted a scenario analysis assuming public funding of DBS for both the procedure and device.

Table 14: Volume of Current Interventions

	Number of procedures performed						
Procedure[a]	2019	2020	2021	2022	Total	Annual average, excluding 2020	%
Gamma Knife radiosurgery	<6	0	<6	<6	<6	1.7	45
RFA	<6	0	<6	<6	6	2.0	55
Total	**<6**	**0**	**<6**	**<6**	**11**	**3.7**	**100**

Abbreviations: RFA, radiofrequency ablation.

[a]Procedures were identified using the following Canadian Classification of Health Interventions (CCI) codes: Gamma Knife radiosurgery was 1AE27JX or 1AN27JX; and RFA was 1AE59SEGX, 1AE59SZGX, 1AE59SZAW, 1AE59SEAW, 1AN59SEAW, 1AN59SEGX, 1AN59SZAW, or 1AN59SZGX.

Source: IntelliHealth Ontario, Inpatient Discharges, 2019–2022, accessed June 22, 2023.

Uptake of the New Intervention and New Intervention Mix

Because MRgFUS neurosurgery does not share the risks of RFA associated with open surgery or the risks of Gamma Knife radiosurgery stemming from ionizing radiation, we conducted the reference case analysis assuming that publicly funded MRgFUS neurosurgery would replace these treatments (N. Lipsman, MD, PhD, email communication, October 9, 2023).

We assumed that all procedures would take place at a large urban teaching hospital with the necessary neurosurgical and psychiatric expertise required to diagnose, treat, and manage patients. Currently, neurosurgical treatment for patients with severe, treatment-refractory OCD largely takes place at 1 site located in Toronto, Ontario. We assumed that in the new scenario, this site would continue to treat patients and would offer MRgFUS neurosurgery to all patients to fully replace RFA; however, a small proportion of patients would be unable to receive MRgFUS neurosurgery due to unamenable skull factors or contraindications to MRI. We assumed that these patients would receive Gamma Knife radiosurgery instead. Therefore, in the new scenario, we assumed that 85% of patients who would usually be treated with RFA or Gamma Knife radiosurgery would instead be treated with MRgFUS neurosurgery, and the remaining 15% would be treated with Gamma Knife radiosurgery (Table 15). We included a scenario analysis in which patients not eligible for MRgFUS neurosurgery in the new scenario would receive RFA instead (Appendix 7, Table A13).

Since 2017, 1 site in Ontario has been treating patients with OCD using MRgFUS neurosurgery as part of a clinical trial through research and philanthropic funding; thus, it is not captured in the administrative data reported in Table 14. The site has treated 32 patients using MRgFUS neurosurgery since 2017, with current annual patient volume closer to 9 to 12 patients (N. Lipsman, MD, PhD, email communication, November 8, 2023). To understand whether this represented a replacement of other types of neurosurgeries, we examined administrative data in Ontario from 2002 to 2022. Prior to the availability of MRgFUS neurosurgery, treatment volumes were consistently no more than 4 patients per year. Thus, we assumed that the 12 patients treated using MRgFUS neurosurgery represented an expansion of the treated population and not a replacement of previously used treatments.

In our reference case, we assumed that this expansion of the population treated with MRgFUS neurosurgery would continue, beginning with the current volume of 12 additional patients in year 1 and linearly increasing to 24 patients in year 5 as awareness spreads, referral patterns are established, and patients and referring physicians are more accepting of a noninvasive surgical option (Table 15). We conducted scenario analyses with different uptake and treatment patterns (Appendix 7, Table A13).

Table 15: Volume of Treatments in the Current and New Scenarios

Scenario	Year 1 (2024)	Year 2 (2025)	Year 3 (2026)	Year 4 (2027)	Year 5 (2028)	Total
Current scenario						
Gamma Knife radiosurgery	2	2	2	2	2	10
RFA	2	2	2	2	2	10
No surgery (expanded population)	12	15	18	21	24	90
New scenario						
Gamma Knife radiosurgery, 15% of original population	1	1	1	1	1	5
RFA, 0%	0	0	0	0	0	0
MRgFUS neurosurgery, 85% of original population + expansion	15	18	21	24	27	105

Abbreviations: MRgFUS, magnetic resonance-guided focused ultrasound; RFA, radiofrequency ablation.

Resources and Costs

Our budget impact analysis includes only costs associated with the health technology from the Ministry of Health perspective:

- Costs of the surgical procedures
- Costs of adverse events
- Ongoing monitoring costs
- Adjunct medication costs

We reported costs in 2023 Canadian dollars and sourced all costs from Ontario data. For instances in which costs were taken from sources not reported in 2023 dollars, we used the all-items Consumer Price Index from Statistics Canada to adjust costs to 2023 dollars.[102] No discounting was applied. We sourced costs for professional services from the Ontario Schedule of Benefits for Physician Services.[103] We based

hospital costs on patient-level costing sourced from the IntelliHealth Ontario portal. We reported costs for DBS in the upcoming tables, but they were only used in a scenario analysis.

A schematic of the included costs by cohort and year is shown in Figure 4.

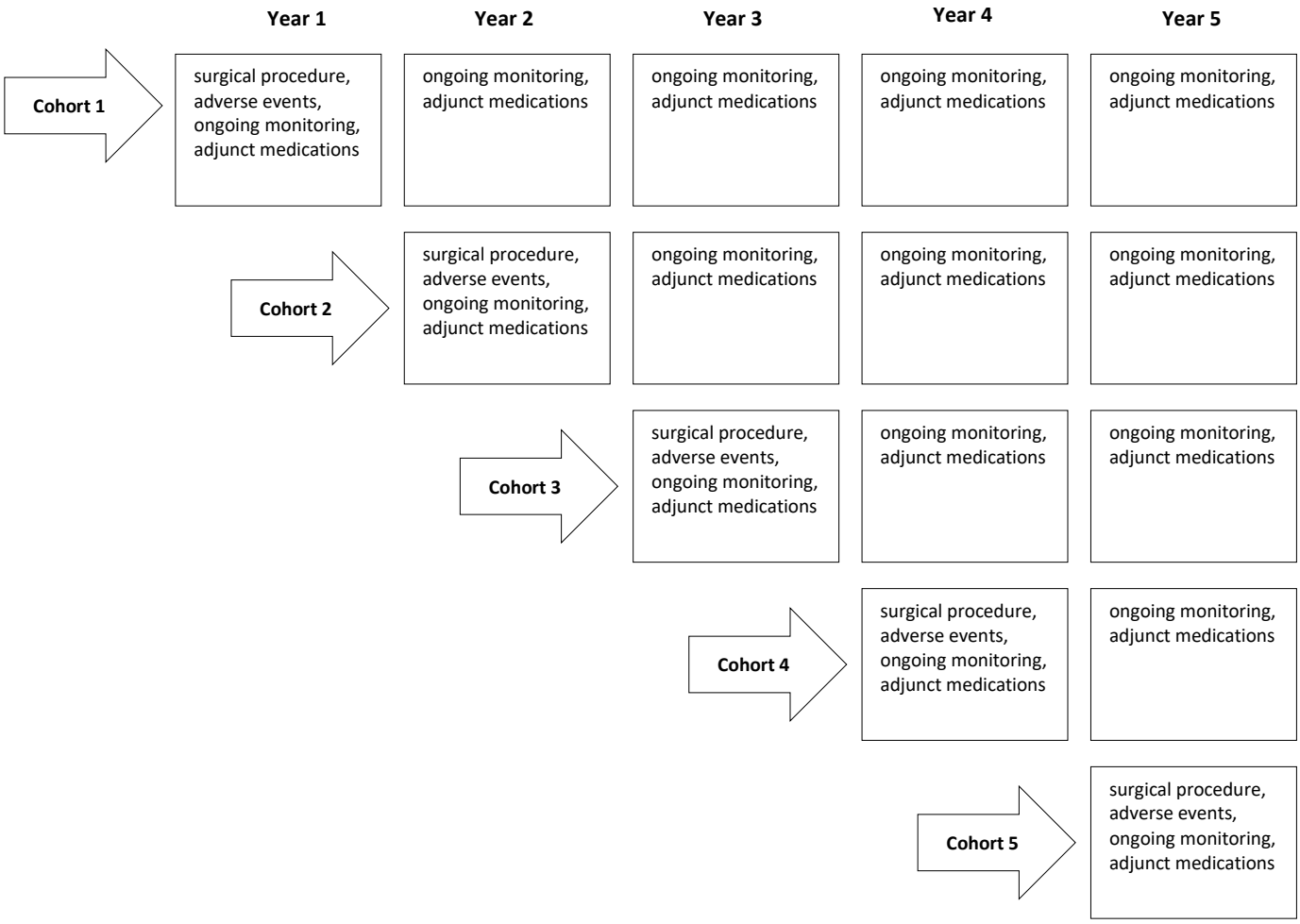

Figure 4: Schematic Model of Costs Included in Budget Impact Analysis

Diagram describing the included costs for each cohort and year of the budget impact analysis. The sum of the columns indicates the total annual costs calculated for each of the current and new scenarios.

Summary of Per-Patient Costs

An overview of the average cost per patient is presented in Table 16. For the first year, average costs ranged from $19,734 for MRgFUS neurosurgery to $743 for patients who did not receive any surgical treatment. Ongoing monitoring and adjunct medication costs are incurred annually in subsequent years as depicted in Figure 4.

Table 16: Total Per-Patient Costs

Cost type	MRgFUS neurosurgery, $[a]	RFA, $[a]	Gamma Knife radiosurgery, $[a]	No surgical treatment, $[a]
Surgical procedure	18,768	11,866	7,084	0
Ongoing monitoring[b]	223	223	223	0
Adjunct medications[b]	743	743	743	743
Adverse events	0	288	1,200	0
Total cost per patient	**19,734**	**13,120**	**9,249**	**743**

Note: Numbers may be inexact due to rounding.

Abbreviations: MRgFUS, magnetic resonance-guided focused ultrasound; RFA, radiofrequency ablation.

[a]All costs are reported in 2023 Canadian dollars.

[b]Costs are incurred annually.

Procedure Costs

Table 17 presents the cost for each surgical procedure. The total mean cost per procedure was $18,768 for MRgFUS neurosurgery, $11,866 for RFA, and $7,084 for Gamma Knife radiosurgery.

We divided procedure costs into preprocedure, periprocedure, and postprocedure costs.

Preprocedure costs include the costs of physician appointments and imaging. We assumed that before undertaking the procedure, all patients would undergo a specialty neurosurgery consultation and a psychiatric consultation. We also assumed that all patients would undergo an MRI and computed tomography (CT) scan prior to surgery.

Periprocedure costs include the inpatient hospital costs (e.g., nursing, radiology, pharmacy, other support services, overhead), physician fees, surgical assistant fees, and anesthesiologist fees. We obtained physician fees from the Ontario Schedule of Benefits for Physician Services.[103] There are no existing fee codes for MRgFUS, RFA, or DBS for the treatment of OCD, so based on consultations with clinical experts, we applied fee code N124, which is for functional stereotaxy for the treatment of movement disorders. This service may be included in an existing insured service or may require its own fee code. Final interpretation of the Schedule of Benefits occurs between the Ministry of Health and the Ontario Medical Association. We estimated inpatient hospital costs using patient-level data from IntelliHealth Ontario by searching for the relevant CCI codes and ICD-10-CA diagnostic codes for OCD (Appendix 7, Table A8). For MRgFUS neurosurgery, inpatient costs were provided by an Ontario hospital currently conducting the procedure (email communication, July 28, 2023).

We excluded capital and fixed costs of MRgFUS equipment purchase, installation, and maintenance in the reference case and assumed that the procedure is performed only in hospitals with pre-existing infrastructure. Currently, there are 2 sites in Ontario with the infrastructure and multidisciplinary expertise required to perform MRgFUS neurosurgery that use equipment that was either donated or purchased by the hospital. The Ministry of Health would be providing funding for operational costs only. Both sites are currently using MRgFUS neurosurgery to treat movement disorders, and 1 site is also treating patients with treatment-refractory OCD. We conducted a scenario analysis that includes capital and fixed costs of the MRgFUS equipment (see Appendix 7, Table A9).

Postprocedure costs include the cost of a follow-up MRI, repeat consultation with a neurosurgeon, and psychiatry consultation.

Table 17: Cost Inputs for Surgical Procedures

Resource item	MRgFUS neurosurgery, $[a]	RFA, $[a]	Gamma Knife radiosurgery, $[a]	DBS, $[a,b]	Data source
Preprocedure					
OHIP professional fees					
Neurosurgery, special surgical consultation	163	163	163	163	Schedule of Benefits[103] (A935)
Psychiatry consultation	223	223	223	223	Schedule of Benefits[103] (A195)
MRI scan – professional fee	73	73	73	73	Schedule of Benefits[103] (X421)
CT scan – professional fee	65	65	65	65	Schedule of Benefits[103] (X401)
Diagnostic procedure costs					
MRI scan – procedure cost	1,397	1,397	1,397	1,397	IntelliHealth Ontario[c] (CCI code: 3.AN.40.^^)
CT scan – procedure cost	856	856	856	856	IntelliHealth Ontario[c] (CCI code: 3.AN.20.^^)
Total preprocedure cost	**2,776**	**2,776**	**2,776**	**2,776**	
Periprocedure					
OHIP professional fees					
Physician fees	2,040[d]	2,040[d]	811	2,040[d]	Schedule of Benefits[103] (N124, X313)
Surgical assistant fees	388	388	0	613	Calculated, see Appendix 7, Table A10
Anesthesiologist fees	573	573	0	852	Calculated, see Appendix 7, Table A11
Inpatient costs					
Device cost	N/A	N/A	N/A	19,100	Ontario hospital currently conducting the procedure[e]
Average total cost per patient	11,240	4,338[f]	1,746[g]	27,557[h]	Ontario hospital currently conducting the procedure[e]; IntelliHealth Ontario[i]; see Appendix 7, Table A8
Total periprocedure cost	**14,241**	**7,339**	**2,557**	**50,162**	
Postprocedure					
OHIP professional fees					
Neurosurgery – repeat consultation	58	58	58	58	Schedule of Benefits[103] (A046)
Psychiatry consultation	223	223	223	223	Schedule of Benefits[103] (A195)
MRI scan – professional fee	73	73	73	73	Schedule of Benefits[103] (X421)
Diagnostic procedure costs					
MRI scan – procedure cost	1,397	1,397	1,397	1,397	IntelliHealth Ontario[c] (CCI code: 3.AN.40.^^)
Total postprocedure cost	**1,751**	**1,751**	**1,751**	**1,751**	
Total cost per procedure	**18,768**	**11,866**	**7,084**	**56,407**	

Note: Numbers may be inexact due to rounding.

Abbreviations: CCI, Canadian Classification of Health Interventions; CT, computed tomography; DBS, deep brain stimulation; MRgFUS, magnetic resonance-guided focused ultrasound; MRI, magnetic resonance imaging; N/A, not applicable; OHIP, Ontario Health Insurance Plan; RFA, radiofrequency ablation.

(notes continued on page 57)

[a]All costs are reported in 2023 Canadian dollars.
[b]For scenario analyses only.
[c]Accessed June 26, 2023.
[d]This service may be included in an existing insured service or may require its own fee code. Final interpretation of the Schedule of Benefits occurs between the Ministry of Health and the Ontario Medical Association.
[e]Email communication, July 28, 2023.
[f]CCI procedure code: 1AN59SEAW, 1AN59SEGX for OCD diagnosis; weighted average of cases from 2017 to 2019, inflated to 2023 Canadian dollars.
[g]CCI procedure code: 1AE27JX, 1AN27JX for OCD diagnosis; weighted average of cases from 2019 to 2022, inflated to 2023 Canadian dollars.
[h]CCI procedure code: 1AE53SEJA, 1AE53SZJA, 1AN53SEJA for OCD diagnoses; weighted average of cases from 2012 to 2019, inflated to 2023 Canadian dollars.
[i]Accessed July 5, 2023.

Cost of Adverse Events

We estimated the costs of managing adverse events by multiplying the expected frequency of adverse events (Table 18) by the management cost per hospitalized adverse event (Table 19) and the percentage of cases that are treated in hospital (Table 20). We included only serious adverse events that required hospitalization. The cost of managing adverse events averaged per person was $0 for MRgFUS neurosurgery, $288 for RFA, and $1,200 for Gamma Knife radiosurgery (Table 20).

The reporting of the frequency of adverse events varied widely across studies. In the absence of meta-analyses, we prioritized studies that were more recent, had larger sample sizes, had longer follow-up time, and used capsulotomy (Table 18). For RFA, we used the frequency of adverse events reported by Liu et al[104] in their 2017 study of 37 patients with OCD treated with RFA. We reviewed additional studies that reported adverse events in patients with OCD treated with RFA and used the minimum and maximum reported values among all 4 publications to calculate the plausible range.[105-107] The frequency of infection for RFA was taken from a study of over 60 patients treated in the US.[108] The frequency of adverse events associated with Gamma Knife radiosurgery was taken from a 2014 randomized controlled trial comparing 12-month outcomes of 8 patients who received Gamma Knife radiosurgery with 8 patients who received a sham procedure (i.e., simulated Gamma Knife radiosurgery using the same equipment).[33] The estimates for the plausible range of frequencies were the minimum and maximum reported values among 3 other studies.[109-111] Although only used for scenario analyses, in Table 17, we present the frequency of adverse events for DBS taken from a recent systematic review and meta-analysis that summarized 34 studies on DBS for treating patients with OCD.[112]

Table 18: Frequency of Adverse Events

Event	Percentage of patients			Source(s)
	Reference case	Plausible range minimum	Plausible range maximum	
MRgFUS neurosurgery				
None	N/A	N/A	N/A	Clinical review
RFA				
Infection	1.6% (1/64)	0.0%	4.8% (1/21)	Montoya et al, 2002[113]; Sheth et al, 2013[108] (reference case)
Cerebral hemorrhage	8.1% (3/37)	0.0%	8.1% (3/37)	Gong et al, 2018[107]; Liu et al, 2008[105]; Liu et al, 2017[104] (reference case); Zhan et al, 2014[106]
Gamma Knife radiosurgery				
Perilesional edema	12.5% (1/8)	0.0%	12.5% (1/8)	Gupta et al, 2019[110]; Lopes et al, 2014[33] (reference case); Peker et al, 2020[111]; Rasmussen et al, 2018[109]
Brain cyst	12.5% (1/8)	2.5% (1/40)	9.1% (5/55)	
DBS[a]				
Infection (surgically treated)	2.0%	N/A	N/A	Gadot et al, 2022[112]
Hardware malfunction	8.0%	N/A	N/A	
Seizure (generalized tonic-clonic)	2.4%	N/A	N/A	
Cerebral hemorrhage (with sequalae)	0.8%	N/A	N/A	

Abbreviations: DBS, deep brain stimulation; MRgFUS, magnetic resonance-guided focused ultrasound; N/A, not applicable; RFA, radiofrequency ablation.

[a]For scenario analysis only.

The hospitalization costs of adverse events were taken from IntelliHealth Ontario inpatient discharge data by ICD-10-CA diagnosis code. Physician costs are not included in the IntelliHealth Ontario data, and the specific physician fee codes used during an adverse event hospitalization are challenging to estimate, as they may differ for each patient depending on the care required. To estimate the physician costs, we adopted the method used in a previously published health technology assessment in which the ratio of the physician costs to hospital costs was estimated using the CIHI patient cost estimator.[114,115] We then obtained physician costs by multiplying the calculated ratio by the hospital costs obtained from IntelliHealth Ontario. When costing data could not be obtained from IntelliHealth Ontario, we used the CIHI patient cost estimator, which included both hospitalization and physician fees. The details for the costing approach are presented in Table 19.

Table 19: Management Cost per Adverse Event Hospitalization

Adverse event	ICD-10-CA diagnosis code	Case mix group number, description	Hospitalization cost, $[a]	Physician cost, $[a]	Total cost, $[a]	Source(s)
Infection	T81.4 (infection following a procedure, not elsewhere classified)	650, multisystemic/unspecified site infection with intervention 32, infection/inflammation of central nervous system except meningitis	18,054	2,677 (using a ratio of 0.15 for physician costs to total costs for the given case mix groups)	20,731	CIHI patient cost estimator[114]; IntelliHealth Ontario[b]
Cerebral hemorrhage	S061 (traumatic cerebral edema)[c]	782, postoperative hemorrhage	10,419	3,935 (using a ratio of 0.38 for physician costs to total costs for the given case mix group)	14,354	CIHI patient cost estimator[114]; IntelliHealth Ontario[b]
Brain cyst	G930 (cerebral cyst)[c]	782, postoperative hemorrhage	5,321	2,010 (using a ratio of 0.38 for physician costs to total costs for the given case mix group)	7,331	CIHI patient cost estimator[114]; IntelliHealth Ontario[b]
Perilesional edema	S061 (traumatic cerebral edema)[c]	782, postoperative hemorrhage	10,419	3,935 (using a ratio of 0.38 for physician costs to total costs for the given case mix group)	14,354	CIHI patient cost estimator[114]; IntelliHealth Ontario[b]
Seizure (generalized tonic-clonic)	N/A	40, seizure disorder except status epilepticus	5,403	1,343	6,746	CIHI patient cost estimator[114]

Note: Numbers may be inexact due to rounding.
Abbreviations: CIHI, Canadian Institute for Health Information; ICD-10-CA, International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada; N/A, not applicable.
[a]All costs are reported in 2023 Canadian dollars.
[b]Accessed November 9, 2023.
[c]Only cases with a main procedure of MRI or CT scan were selected to estimate the average cost.

The total cost of managing adverse events was averaged per person by multiplying the frequency of adverse events (Table 18) by the cost of managing the adverse event in the hospital (Table 19) and the percentage of cases that would be managed for that adverse event in the hospital (Table 20).

Table 20: Costs of Managing Adverse Event Hospitalizations

Adverse event	Reference case, $[a]	Plausible range minimum, $[a]	Plausible range maximum, $[a]	Treatment assumptions	Source(s)
MRgFUS neurosurgery					
No adverse events reported	N/A	N/A	N/A		Clinical review
Average total per-person cost of managing adverse events	**0.00**	**0.00**	**0.00**		

Adverse event	Reference case, $[a]	Plausible range minimum, $[a]	Plausible range maximum, $[a]	Treatment assumptions	Source(s)
RFA					
Infection	32.39	0.00	98.72	10% of patients require hospitalization; the remaining 90% of patients are treated with antibiotics as outpatients[b]	CIHI patient cost estimator[114]; IntelliHealth Ontario[c]; Montoya et al, 2002[113]; Sheth et al, 2013[108]
Cerebral hemorrhage	256.05	0.00	256.05	22% (8/37) of cases are symptomatic[116] and are hospitalized for close monitoring and blood pressure control[b]	CIHI patient cost estimator[114]; Gong et al, 2018[107]; Horisawa et al, 2021[116]; IntelliHealth Ontario[c]; Liu et al, 2008[105]; Liu et al, 2017[104]; Zhan et al, 2014[106]
Average total per-person cost of managing adverse events	**288.44**	**0.00**	**354.77**		
Gamma Knife radiosurgery					
Brain cyst	302.39	60.48	302.39	33% of cysts are symptomatic,[109] require hospitalization, and are managed with inpatient observation[b]	CIHI patient cost estimator[114]; Gupta et al, 2019[110]; IntelliHealth Ontario[c]; Lopes et al, 2014[33]; Peker et al, 2020[111]; Rasmussen et al, 2018[109]
Perilesional edema	897.15	0.00	897.15	50% of patients are treated in the hospital[b]	CIHI patient cost estimator[114]; Gupta et al, 2019[110]; IntelliHealth Ontario[c]; Lopes et al, 2014[33]; Peker et al, 2020[111]; Rasmussen et al, 2018[109]
Average total per-person cost of managing adverse events	**1,199.53**	**60.48**	**1,199.53**		
DBS					
Infection (surgically treated)	414.61	N/A	N/A	All surgically treated infections are managed in the hospital	CIHI patient cost estimator[114]; Gadot et al, 2022[112]; IntelliHealth Ontario[c]
Hardware malfunction	2,979.57	N/A	N/A	All hardware malfunctions require a reoperation[117]	Fenoy and Simpson, 2014[117]; Gadot et al, 2022[112]
Seizure (generalized tonic-clonic)	161.91	N/A	N/A	All seizure disorders require 1 hospitalization	CIHI patient cost estimator[114]; Gadot et al, 2022[112]
Cerebral hemorrhage (with sequalae)	114.83	N/A	N/A	All cerebral hemorrhage with sequalae require hospitalization	CIHI patient cost estimator[114]; Gadot et al, 2022[112]; IntelliHealth Ontario[c]
Average total per-person cost of managing adverse events	**3,670.94**	**N/A**	**N/A**		

Note: Numbers may be inexact due to rounding.

Abbreviations: CIHI, Canadian Institute for Health Information; DBS, deep brain stimulation; MRgFUS, magnetic resonance-guided focused ultrasound; N/A, not applicable; RFA, radiofrequency ablation.

[a]All costs are reported in 2023 Canadian dollars.

[b]B. Davidson, MD, email communication, November 8, 2023.

[c]Accessed November 9, 2023.

Ongoing Monitoring Costs

We assumed that anyone who underwent a neurosurgical procedure would have an annual psychiatry consultation for at least 5 years (Table 21).

Table 21: Ongoing Monitoring Costs Following Surgical Procedures

Resource item	Unit cost, $[a]	Number of visits per year	Total cost, $[a]	Data source and comments
MRgFUS neurosurgery				
Psychiatry consultation	222.50	1	222.50	Schedule of Benefits[103] (A195)
RFA				
Psychiatry consultation	222.50	1	222.50	Schedule of Benefits[103] (A195)
Gamma Knife radiosurgery				
Psychiatry consultation	222.50	1	222.50	Schedule of Benefits[103] (A195)
DBS				
First year following surgery				
Clinical programming of deep brain stimulator, 2 implantation sites	343.55	1	343.55	Schedule of Benefits[103] (G547, G549)
Subsequent years following surgery				
Clinical programming of deep brain stimulator, 2 implantation sites	343.55	2	687.10	Schedule of Benefits[103] (G547, G549)

Note: Numbers may be inexact due to rounding.

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

[a]All costs are reported in 2023 Canadian dollars.

Adjunct Medication Costs

Although we assumed that there would be no changes to medication usage in the reference case, we describe the process of estimating medication costs for scenario analyses. We ran a scenario analysis in which medications are reduced for all types of neurosurgeries such that medication costs decrease by 25%,[109,118] but there are no changes in medication usage or cost for those who do not receive neurosurgery.

We estimated the cost of medications for the patients with OCD reported in the 2020 publication by Davidson et al[72] (Appendix 7, Table A12). Medications were costed using the Ontario Drug Benefit Formulary[119] with the reported amount paid for by the Ministry of Health plus an 8% markup.[120]

The average annual cost of medications was almost $900 and ranged from $0 to approximately $1,850. In Ontario, medication costs are covered via the Ontario Drug Benefit (ODB) program for qualifying patients. Ontarians may be eligible for ODB if they are 65 years or older, 24 years or younger with no private insurance, living in long-term care, receiving benefits from Ontario Works or the Ontario Disability Support Program (ODSP), or enrolled in the Trillium Drug Program.[121]

We estimated the proportion of the population with medication coverage using the mean age reported in the clinical trials and reports of disability coverage. The mean age of patients with OCD in the clinical trials was less than 65 years (Table 3). The MRgFUS neurosurgery clinical trials did not report demographic characteristics that could inform whether participants were receiving benefits (e.g.,

socioeconomic status, disability status), such as those from Ontario Works or ODSP. However, Lee et al[122] conducted a trial on 5 cases of DBS for patients with treatment-refractory OCD in Ontario between 2010 and 2015, and they reported that 80% of patients were receiving disability benefits. Therefore, we assumed that 80% of patients receiving neurosurgery for OCD are eligible for ODB and included their medication costs in the Ministry of Health perspective. We applied this percentage to the average cost of medications calculated from the publication by Davidson et al[72] and added dispensing fees, assuming that medications would be dispensed 4 times per year with an average dispensing fee of $10, giving an average per-person annual medication cost of $743.

Internal Validation

The secondary health economist (HAT) conducted formal internal validation. This process included checking for errors and ensuring the accuracy of parameter inputs and equations in the budget impact analysis.

Analysis

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. We also conducted sensitivity analyses to explore how the results are affected by varying input parameters and model assumptions. We used Microsoft Excel to code the budget impact analysis model.[92]

We conducted the following sensitivity or scenario analyses:

- Scenario 1, population of interest: We used the population of interest estimated by epidemiological parameters (Table 13) as the total population to represent an upper bound on the volume of the intervention. For the current scenario, we assumed that the number of people accessing RFA and Gamma Knife radiosurgery stays the same and the remaining people receive no surgical treatment (Appendix 7, Table A13).
- Scenario 2, increased expansion of MRgFUS neurosurgery: We assumed that the population would expand by an additional 12 nonsurgically treated people receiving MRgFUS neurosurgery in year 1, increasing linearly to 30 additional people in year 5 (Appendix 7, Table A13).
- Scenario 3, steady but slower expansion of MRgFUS neurosurgery: We assumed that the population would expand by an additional 12 nonsurgically treated people per year accessing MRgFUS neurosurgery (Appendix 7, Table A13).
- Scenario 4, steady but increased expansion of MRgFUS neurosurgery: We assumed that the population would expand by an additional 24 nonsurgically treated people per year accessing MRgFUS neurosurgery (Appendix 7, Table A13).
- Scenario 5, decreased Gamma Knife radiosurgery: We explored a scenario in which MRgFUS technology has improved and obviates the need for Gamma Knife radiosurgery by reducing the percentage of people receiving Gamma Knife radiosurgery each year in the new scenario from 15% to 0% (Appendix 7, Table A13).

- Scenario 6, patients not eligible for MRgFUS neurosurgery receive RFA: We assumed that people who are not eligible for MRgFUS neurosurgery in the new scenario will receive RFA (Appendix 7, Table A13).
- Scenario 7, public funding includes capital costs (average patient volume): We included capital expenditures of MRgFUS neurosurgery in the total cost of MRgFUS neurosurgery (Appendix 7, Table A9).
- Scenario 8, public funding includes capital costs (low patient volume): We included capital expenditures of MRgFUS neurosurgery in the total cost of MRgFUS neurosurgery, assuming an annual caseload of 60 patients (48 with essential tremor and 12 with OCD).
- Scenario 9, public funding includes capital costs (high patient volume): We included capital expenditures of MRgFUS neurosurgery in the total cost of MRgFUS neurosurgery, assuming an annual caseload of 78 patients (48 with essential tremor and 30 with OCD).
- Scenario 10, medication costs decrease by 25%: We explored the impact of a reduction in medication usage after neurosurgery by reducing the medication costs for people who received neurosurgery by 25% (Appendix 7, Table A12).
- Scenario 11, re-treatment for MRgFUS neurosurgery with Gamma Knife radiosurgery: We examined the impact of 10% of patients treated with MRgFUS neurosurgery requiring re-treatment with Gamma Knife radiosurgery due to failure to create a lesion with MRgFUS neurosurgery. To calculate the cost of re-treatment, we estimated the number of patients who fail treatment by multiplying the number of patients treated with MRgFUS neurosurgery by the failure rate of MRgFUS neurosurgery and then multiplying the resulting number of patients by the procedure cost of Gamma Knife radiosurgery.
- Scenario 12, re-treatment for MRgFUS neurosurgery with RFA: We examined the impact of 10% of patients treated with MRgFUS neurosurgery requiring re-treatment with RFA due to failure to create a lesion with MRgFUS neurosurgery. To calculate the cost of re-treatment, we estimated the number of patients who fail treatment by multiplying the number of patients treated with MRgFUS neurosurgery by the failure rate of MRgFUS neurosurgery and then multiplying the resulting number of patients by the procedure cost of RFA.
- Scenario 13, decreased inpatient procedure cost of MRgFUS neurosurgery: We examined the impact of decreasing the inpatient procedure costs of MRgFUS neurosurgery by 20% from $11,240 to $8,992, making the total procedure cost $16,520 instead of the reference case value, $18,768.
- Scenario 14, increased inpatient procedure cost of MRgFUS neurosurgery: We examined the impact of increasing the inpatient procedure costs of MRgFUS neurosurgery by 20% from $11,240 to $13,488, making the total procedure cost $21,016 instead of the reference case value, $18,768.
- Scenario 15, decreased inpatient procedure cost of RFA: We examined the impact of lower inpatient procedure costs for RFA by using the lower 95% confidence interval estimate from the IntelliHealth Ontario data (Appendix 7, Table A8), $1,256, rather than the mean, $4,338, making the total procedure cost $8,784 instead of the reference case value, $11,866.

- Scenario 16, increased inpatient procedure cost of RFA: We examined the impact of higher inpatient procedure costs for RFA by using the upper 95% confidence interval estimate from the IntelliHealth Ontario data (Appendix 7, Table A8), $7,420, rather than the mean, $4,338, making the total procedure cost $14,945 instead of the reference case value, $11,866.
- Scenario 17, decreased inpatient procedure cost of Gamma Knife radiosurgery: We examined the impact of lower inpatient procedure costs for Gamma Knife radiosurgery by using the lower 95% confidence interval estimate from the IntelliHealth Ontario data (Appendix 7, Table A8), $1,583, rather than the mean, $1,746, making the total procedure cost $6,921 instead of the reference case value, $7,084.
- Scenario 18, increased inpatient procedure cost of Gamma Knife radiosurgery: We examined the impact of higher inpatient procedure costs for Gamma Knife radiosurgery by using the upper 95% confidence interval estimate from the IntelliHealth Ontario data (Appendix 7, Table A8), $1,908, rather than the mean, $1,746, making the total procedure cost $7,247 instead of the reference case value, $7,084.
- Scenario 19, lower estimate of RFA adverse event costs: We examined the impact of the cost of adverse events of RFA by calculating costs using the upper estimates for the plausible range of frequency of adverse events (Tables 18 and 20).
- Scenario 20, upper estimate of RFA adverse event costs: We examined the impact of the cost of adverse events of RFA by calculating costs using the lower estimates for the plausible range of frequency of adverse events (Tables 18 and 20).
- Scenario 21, lower estimate of Gamma Knife radiosurgery adverse event costs: We examined the impact of the cost of adverse events of Gamma Knife radiosurgery by calculating costs using the upper estimates for the plausible range of frequency of adverse events (Tables 18 and 20).
- Scenario 22, no anesthesiologist costs for MRgFUS neurosurgery: We examined the impact of eliminating the cost of an anesthesiologist for neurosurgical procedures that do not require general anesthesia.
- Scenario 23, alternate fee code for Gamma Knife radiosurgery: We examined the impact of physician fees for Gamma Knife radiosurgery being compensated using fee code N124 and including costs for a surgical assistant and anesthesiologist. The total procedure cost increased from $7,084 to $9,610.
- Scenario 24, public funding of DBS and replacement of DBS by MRgFUS neurosurgery: We examined the impact of simultaneous public funding of DBS and replacement of DBS by MRgFUS neurosurgery in the new scenario. We estimated that 2 people per year would receive DBS under public funding in the current scenario based on historical volumes of neurosurgery for severe, treatment-refractory OCD and assumed that they would receive MRgFUS neurosurgery in the new scenario. The costs of DBS are reported in Tables 17, 20, and 21.
- Scenario 25, increase in physician fees: We examined the impact of a 4% increase in all physician fees.

Results

Reference Case

We estimated that publicly funding MRgFUS neurosurgery for severe, treatment-refractory OCD would incur an additional $251,601 in year 1 and increase to an additional $494,174 in year 5, for a total budget impact of $1,861,100 over the next 5 years (Table 22). The budget increase is mainly a result of more patients accessing treatment. In the new scenario, 110 patients would receive neurosurgical treatment over 5 years, whereas in the current scenario, only 20 patients receive neurosurgery, meaning 90 additional people would access neurosurgical treatment. The largest component of the budget impact is the additional cost of the surgical procedure, which accounts for $1,816,582 of the 5-year budget impact and represents about 98% of the total budget. Over the 5 years, there would also be increased costs of $53,400 for monitoring patients. Replacing RFA and Gamma Knife radiosurgery with MRgFUS neurosurgery (a noninvasive procedure that does not use ionizing radiation) would result in fewer serious adverse events and save $8,882 in adverse event costs over 5 years. Results stratified by intervention are presented in Appendix 7, Table A14.

Table 22: Budget Impact Analysis Results – Reference Case

	Budget impact, $[a]					
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total[b,c]**
Current scenario						
Surgical procedure costs	37,900	37,900	37,900	37,900	37,900	**189,498**
Monitoring costs	890	1,780	2,670	3,560	4,450	**13,350**
Adjunct medication costs	11,888	26,006	42,352	60,928	81,732	**222,906**
Adverse event costs	2,976	2,976	2,976	2,976	2,976	**14,880**
Total cost of current scenario	**53,654**	**68,661**	**85,898**	**105,363**	**127,058**	**440,634**
New scenario						
Surgical procedure costs	288,607	344,911	401,216	457,520	513,825	**2,006,079**
Monitoring costs	3,560	7,788	12,683	18,245	24,475	**66,750**
Adjunct medication costs	11,888	26,006	42,352	60,928	81,732	**222,906**
Adverse event costs	1,200	1,200	1,200	1,200	1,200	**5,998**
Total cost of new scenario	**305,255**	**379,904**	**457,450**	**537,893**	**621,232**	**2,301,733**
Budget impact[b,c]						
Surgical procedure costs	250,707	307,012	363,316	419,621	475,925	**1,816,582**
Monitoring costs	2,670	6,008	10,013	14,685	20,025	**53,400**
Adjunct medication costs	0	0	0	0	0	**0**
Adverse event costs	−1,776	−1,776	−1,776	−1,776	−1,776	**−8,882**
Total budget impact	**251,601**	**311,243**	**371,552**	**432,529**	**494,174**	**1,861,100**

[a]All costs are reported in 2023 Canadian dollars.

[b]Negative costs indicate savings.

[c]Results may appear inexact due to rounding.

Sensitivity Analysis

The results of the 25 scenario analyses are presented in Table 23. Compared with the reference case, scenarios in which the costs of RFA or Gamma Knife radiosurgery increased, cost of MRgFUS neurosurgery decreased, medications costs were reduced, or treatment volume was less than the reference case resulted in a lower budget impact. Scenarios in which costs of RFA or Gamma Knife radiosurgery decreased, cost of MRgFUS neurosurgery increased, capital or re-treatment costs for MRgFUS neurosurgery were included, or treatment volume was greater than the reference case resulted in a higher budget impact compared with the reference case.

Overall, treatment volume (the number of treated patients in the new scenarios) resulted in the largest changes to the budget impact. In the reference case, the number of patients treated with neurosurgery in the new scenario was 110 over 5 years. For scenarios 1 to 4, the number of surgically treated patients in the new scenario ranged from 80 (scenario 3, steady but slower expansion of MRgFUS neurosurgery) to 217 (scenario 1, population of interest). The 5-year budget impact ranged from $1,240,123 (scenario 3) to $3,945,836 (scenario 1).

Table 23: Budget Impact Analysis Results – Scenario Analyses

Scenario	Budget impact, $[a]						% change[c]	Total number of surgically treated patients in new scenario
	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b]		
Reference case	251,601	311,243	371,552	432,529	494,174	1,861,100	—	110
Scenario 1, population of interest	745,359	772,804	781,482	809,150	837,041	3,945,836	112%	217
Scenario 2, increased expansion of MRgFUS neurosurgery	251,601	350,710	432,685	536,026	622,232	2,193,253	18%	126
Scenario 3, steady but slower expansion of MRgFUS neurosurgery	251,601	252,042	250,254	246,236	239,990	1,240,123	−33%	80
Scenario 4, steady but increased expansion of MRgFUS neurosurgery	488,405	500,432	510,231	517,800	523,140	2,540,008	36%	140
Scenario 5, decreased Gamma Knife radiosurgery	262,086	321,728	382,037	443,014	504,659	1,913,524	3%	110
Scenario 6, patients not eligible for MRgFUS neurosurgery receive RFA	255,472	315,114	375,423	436,401	498,045	1,880,455	1%	110
Scenario 7, public funding includes capital costs (average patient volume)	420,664	514,119	608,242	703,031	798,489	3,044,546	64%	110
Scenario 8, public funding includes capital costs (low patient volume)	437,571	534,407	631,911	730,082	828,920	3,162,890	70%	110
Scenario 9, public funding includes capital costs (high patient volume)	394,655	482,908	571,828	661,416	751,671	2,862,477	54%	110
Scenario 10, medication costs decrease by 25%	248,629	304,741	360,964	417,298	473,741	1,805,373	−3%	110
Scenario 11, 10% of patients treated with MRgFUS neurosurgery require re-treatment with Gamma Knife radiosurgery	262,226	311,243	371,552	432,529	494,174	1,871,725	1%	110
Scenario 12, 10% of patients treated with MRgFUS neurosurgery require re-treatment with RFA	269,400	311,243	371,552	432,529	494,174	1,878,899	1%	110
Scenario 13, decreased inpatient procedure cost of MRgFUS neurosurgery	217,881	270,779	324,344	378,577	433,478	1,625,058	−13%	110
Scenario 14, increased inpatient procedure cost of MRgFUS neurosurgery	285,321	351,707	418,761	486,482	554,870	2,097,141	13%	110
Scenario 15, decreased inpatient procedure cost of RFA	257,765	317,407	377,716	438,693	500,338	1,891,919	2%	110
Scenario 16, increased inpatient procedure cost of RFA	245,437	305,079	365,389	426,366	488,010	1,830,280	−2%	110
Scenario 17, decreased inpatient procedure cost of Gamma Knife radiosurgery	255,179	314,821	375,131	436,108	497,752	1,878,991	1%	110
Scenario 18, increased inpatient procedure cost of Gamma Knife radiosurgery	251,438	311,080	371,390	432,367	494,011	1,860,286	0%[d]	110
Scenario 19, lower estimate of RFA adverse event costs	252,178	311,820	372,129	433,106	494,751	1,863,984	0%[d]	110
Scenario 20, upper estimate of RFA adverse event costs	251,468	311,110	371,420	432,397	494,041	1,860,436	0%[d]	110
Scenario 21, lower estimate of Gamma Knife radiosurgery adverse event costs	252,740	312,382	372,691	433,669	495,313	1,866,795	0%[d]	110
Scenario 22, no anesthesiologist costs for MRgFUS neurosurgery	243,004	300,926	359,517	418,774	478,700	1,800,921	−3%	110

Scenario	Budget impact, $[a]						% change[c]	Total number of surgically treated patients in new scenario
	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b]		
Scenario 23, alternate fee code for Gamma Knife radiosurgery	249,075	308,771	369,026	430,004	491,648	1,848,470	−1%	110
Scenario 24, public funding of DBS and replacement of DBS by MRgFUS neurosurgery	168,730	214,068	257,845	300,061	340,715	1,281,419	−31%	120
Scenario 25, increase in physician fees	253,638	313,879	374,814	436,444	498,768	1,877,543	1%	110

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

[a]All costs are reported in 2023 Canadian dollars.

[b]Results may appear inexact due to rounding.

[c]Percent change calculated as the difference in the total budget impact of the scenario analysis and the total budget impact of the reference case divided by the total budget impact of the reference case.

[d]Percent change was very small (<0.5%).

Discussion

In this budget impact analysis, we estimated the costs required to publicly fund MRgFUS neurosurgery for adults with severe, treatment-refractory OCD. We found that publicly funding this intervention would result in a $1.9 million increase in the budget over 5 years for 110 people to receive neurosurgical treatment over the same 5-year period.

In our reference case, we assumed that the number of people surgically treated over 5 years increases from 20 to 110 with public funding of MRgFUS neurosurgery. MRgFUS is the only neurosurgical option that is noninvasive and does not use ionizing radiation, eliminating the potential risks related to general anesthesia and open surgery in RFA and the potential risks related to exposure to ionizing radiation in Gamma Knife radiosurgery.[33,104-107,109-111] We assumed that this would lead to more interest and acceptance of a surgical option. MRgFUS neurosurgery is performed in an MRI suite rather than an operating room; thus, it would not use limited operating room time. Additionally, the procedure requires a 1-night hospital stay, unlike RFA in which hospital stays ranged from 1 to 3 days (see Appendix 7, Table A8).

Only 2 sites in Ontario currently have the equipment necessary to perform these interventions. Through consultation with clinical experts, we do not foresee a capacity issue; however, there may be geographical inequity, as people living farther from the sites would be required to travel for the procedure.

Strengths and Limitations

Our analysis was strengthened by continuous engagement with clinical experts currently performing MRgFUS neurosurgery who confirmed and helped inform key model parameters and assumptions. Additionally, we ran extensive scenario analyses to determine the impact of our assumptions and uncertainty in key parameters.

The following limitations should be noted when interpreting the findings of this analysis. Inpatient procedure costs for RFA and Gamma Knife radiosurgery were sourced from administrative data, but there were few procedures to treat OCD, so there was a lot of uncertainty in the costs. The inpatient procedure costs were likely underestimated. When administrative data were used to estimate the inpatient procedure cost of MRgFUS neurosurgery, the cost was much lower than the value provided directly from a centre currently performing the procedure. We believe that the cost estimate for MRgFUS neurosurgery provided from the centre is most accurate, and we used it in our analysis. Similar estimates for RFA and Gamma Knife radiosurgery were not available, and we used the best available evidence. In our sensitivity analyses, the inpatient procedure costs for RFA and Gamma Knife radiosurgery were demonstrated to have little effect on the budget impact due to the low number of RFA and Gamma Knife procedures.

Our analysis did not account for potential changes in health care use such as doctor's visits, emergency department visits, or hospitalizations. Furthermore, many of the costs of OCD fall on the patient and are not within the Ministry of Health perspective, such as psychotherapy and lost workdays.

Conclusions

- We expect public funding of MRgFUS neurosurgery for treatment-refractory OCD in Ontario to result in an additional increase in budget of $1.9 million and 110 patients receiving neurosurgical treatment over 5 years.
- Patient volume and potential public funding of capital costs had the largest impact on the budget.

Preferences and Values Evidence

Objective

The objective of this analysis was to explore the underlying values, needs, and priorities of those who have lived experience of obsessive–compulsive disorder (OCD), as well as the preferences and perceptions of patients, family, and care partners of magnetic resonance-guided focused ultrasound (MRgFUS) neurosurgery for the treatment of people with treatment-refractory OCD.

Background

Exploring patient preferences and values provides a unique source of information about people's experiences of a health condition and the health technologies or interventions used to manage or treat that health condition. It includes the impact of the condition and its treatment on the person with the health condition, their family and other care partners, and the person's personal environment. Engagement also provides insight into how a health condition is managed by the province's health system.

Information shared from lived experience can also identify gaps or limitations in published research (e.g., outcomes important to those with lived experience that are not reflected in the literature).[123-125] Additionally, lived experience can provide information and perspectives on the ethical and social values implications of health technologies.

Because the needs, preferences, priorities, and values of those with lived experience in Ontario are important to consider and to understand the impact of the technology in people's lives, we may speak directly with people who live with a given health condition, including those with experience of the technology or intervention we are exploring.

For this analysis, we examined the preferences and values of people with lived experience of OCD via direct engagement. The initiative was led by the Patient and Public Partnering team at Ontario Health, and direct engagement with eligible participants was completed through telephone interviews.

Direct Patient Engagement

Methods

Partnership Plan

The partnership plan for this health technology assessment focused on consultation to examine the experiences of people with OCD and those of their families and other care partners. We engaged people via telephone interviews.

We used a qualitative interview, as this method of engagement allowed us to explore the meaning of central themes in the experiences of people with OCD, their journey to diagnosis, and the experiences of their families and care partners.[126] The sensitive nature of exploring people's experiences of a health condition and their quality of life further supported our choice of methodology.

Participant Outreach

We used an approach called purposive sampling,[127-130] which involves actively reaching out to people with direct experience of the health condition and health technology or intervention being reviewed. We approached the MRgFUS neurosurgery centre at a hospital in Toronto, Ontario, in an effort to engage with patients who have undergone or are on the waitlist for the procedure.

Inclusion Criteria

We sought to speak with adults with lived experience of OCD who underwent or may undergo MRgFUS neurosurgery. People did not need to have direct experience with MRgFUS neurosurgery in order to participate.

Exclusion Criteria

We did not set exclusion criteria for participants who otherwise met the inclusion criteria.

Participants

For this project, we spoke to a total of 14 participants. Nine of the 14 participants were diagnosed with OCD, and the other 5 participants were care partners of people with OCD. Of the 9 patients who were interviewed, 6 had experience with MRgFUS neurosurgery and 3 were on the waitlist.

Approach

At the beginning of the interview, we explained the role of our organization, the purpose of this health technology assessment, the risks of participation, and how participants' personal health information would be protected. We gave this information to participants both verbally and in a letter of information (Appendix 8) if requested. We then obtained participants' verbal consent before starting the interview. With participants' consent, we audio-recorded and then transcribed the interviews.

Interviews lasted approximately 30 to 60 minutes. The interview was semistructured and consisted of a series of open-ended questions. Questions were based on a list developed by the Health Technology Assessment International Interest Group on Patient and Citizen Involvement in Health Technology Assessment.[131] Questions focused on the impact of OCD on quality of life, the journey to diagnosis, experience with MRgFUS neurosurgery, and the impact of MRgFUS neurosurgery. Please see Appendix 9 for our interview guide.

Data Extraction and Analysis

We used a modified version of a grounded-theory methodology to analyze interview transcripts. This approach allowed us to organize and compare information on experiences across participants. This method consists of a repetitive process of obtaining, documenting, and analyzing responses while simultaneously collecting, analyzing, and comparing information.[132,133] We used the qualitative data analysis software program NVivo[134] to identify and interpret patterns in the data. The patterns we identified allowed us to describe the impact of OCD on the patient's life and decision-making factors for MRgFUS neurosurgery.

Results

Living With OCD

Participants with OCD described experiencing different symptoms, including obsessive, intrusive thoughts that trigger distress as well as compulsive behaviours performed in an attempt to stop the obsessive thoughts or decrease distress. These symptoms were persistent and impacted different aspects of their daily lives.

> *My physical compulsions are very minimized, but my mental compulsions are way through the roof and very debilitating. I call them spikes. So, if I have an OCD spike, [if I have a] random intrusive thought roll in, my brain goes, "Oh God, that's horrible. We need to focus on that," even though, logically, I know that it's not a problem.*

> *I started having intrusive song lyrics playing in my head 24/7. It's a common experience for anyone from time to time to get a song stuck in their head, right? Like an earworm, but mine were super intrusive, super constant, very loud. It was almost as if I had this kind of crazy stereo in my head that just wouldn't shut up. It was really horrible.*

> *I'm struggling with contamination issues. Symptoms are hand washing and ruminations.*

> *My school desk always had to be perfectly organized, and if someone moved something, I had to do a lot of reorganizing stuff.*

Most participants with OCD started showing symptoms as a child and were formally diagnosed with OCD as a child or adolescent.

> *My OCD journey started when I was around 6, but I didn't get formally diagnosed until I was around 11 or 10.*

> *I remember things really started to show in terms of my OCD when I started grade 9 in 2008. I was 14 years old at the time.*

Impact on Day-to-Day Life

Participants described the effect that OCD had on their day-to-day life, including difficulty performing activities such as eating, showering, leaving the house, and doing household chores.

> *Sometimes he'll go 3 or 4 days without getting up to even eat or drink or do anything.*

> *Leaving the house or my apartment on my own is impossible because OCD just completely takes over.*

> *I stopped showering every day and say, "Oh, well, it doesn't matter if you don't do it. Just go to work anyway." I wouldn't brush my teeth every day. I sleep on the couch instead of in my bed.*

> *It was so hard to [fold] laundry. Usually, I just [keep my washed clothes in] the dryer machine. Other times, there are periods where it [laundry] would be on my bed for months at a time.*

Participants with OCD also mentioned that it takes them longer to complete tasks that would otherwise be completed in shorter periods owing to their tendency to repeat the same task multiple times before feeling satisfied.

> *I remember I spent like 40 minutes loading and unloading [the] dishwasher. I just couldn't get it right. Then I broke down calling my mom.*

> *I have problems reading where I'll read the sentence in a paragraph and then I lose where I am in the sentence and then I have to start over again at the beginning of the sentence.*

Impact on Work and School

Participants explained that their OCD symptoms contributed to decreased productivity and performance at work, as well as repercussions in their career path. Most of them had to quit their jobs altogether because their symptoms were persistent and prevented them from working.

> *Currently [I'm in my 20s], I'm not working. I'm unable to work mostly because of my OCD.*

> *She lost her job as a dental hygienist because she couldn't do that work anymore.*

> *If I worked, I would basically not be able to work really well because I have to repeat tasks and it would take me forever to do it.*

> *He was working his way up [in his career]. But the OCD just kept him from progressing. It [OCD] was always there, nagging at him. There were various times where he would spend hours sitting in the car because he couldn't leave his vehicle.*

Participants also mentioned that OCD negatively affected their pursuit of education, such that it took them longer to complete or couldn't complete their program. In turn, this also impacted their ability to pursue a career.

> *It took me 6 years to do a 2-year program because I'm used to repeating things.*

> *I had to drop out of school.*

Impact on Social Life and Family Relationships

Participants' social life and family relationships were also impacted by their OCD symptoms. Participants explained that they had limited social interactions with their friends and families due to their symptoms. This made it difficult to engage with others and form relationships. Some mentioned having social anxiety.

> *He has no social life. He does not talk to his friends. He does not talk to family members. He barely talks to me. It's very severe.*

> *I would say it impacts his social life immensely. He has social anxiety as well, so a lot of his mental compulsions are around social interactions.*

I have social anxiety. When I go out to meet new people, a lot of the time I become too anxious and I can't come up with anything to say back to the person, so I create awkward situations.

Participants mentioned that OCD affected their family dynamics and strained their relationships with family members and friends.

It [OCD] changed my family dynamics. Before I was diagnosed, I had good relationship[s] with my sister and my parents, but as I got diagnosed and I became more severe as time went by, my parents have to focus on me a lot and that caused my sister to be quite lonely.

[OCD has] strained friendships, [it has] strained relationships. When my OCD symptoms really started to deteriorate, [it affected my relationships].

Impact on Mental Health

Mental health was emphasized as being substantially impacted by OCD. Participants reported that their mental health disorders, including anxiety and depression, were associated with their OCD. Furthermore, most participants reported struggling with suicidal thoughts.

Along with his OCD, he's been diagnosed with having major depressive disorder.

I have a major problem with depression and anxiety.

I also developed a lot of suicidal ideation and suicidal thoughts.

I feel there's sometimes no hope for me, that I'm going to be like this forever, and a lot of times, I feel like committing suicide because of that.

Some participants experienced lack of sleep, which further exacerbated their mental health problems.

I think OCD is the driver which really contributed to my lack of sleep and depression.

I'm always going through my list and it's hard to sleep. I haven't slept for the last 3 days.

Impact on Care Partners

Care partners, which are mostly family members of people with OCD, reported the substantial impact that caring for someone with OCD has on different aspects of their lives, including social, mental, professional, and financial aspects. Care partners spoke about feeling socially isolated due to their overwhelming care duties. They also reported increased anxiety and stress leading to repercussions in their career. Furthermore, most care partners mentioned the financial burden that comes with taking care of a loved one with OCD, as they become the sole financial provider.

I have no family or friends that come into the house anymore because my son basically sleeps on the couch in the dining room.

His suicide attempts also negatively impacted all of us … I've been clinically diagnosed with PTSD.

I had a nervous breakdown about a year and a half ago, and I'm now out of work. I had to quit my job.

If he gets the surgery, we'll be going down to Toronto, and this will be on my dime. So, financially it's been a lot because I try and help him with food payments and buying him whatever he needs.

Patients also reflected the reliance they had on their care partners (family members) due to their OCD symptoms.

My parents had to once again take care of me as if I was a child and dedicate a lot of their time to support me and keep me safe, given the suicidal ideation I was having.

It puts a lot of stress on my dad because he can't always be there for me because he's busy with work.

Treatment

Participants spoke about their journey of trying different treatment options for OCD, including medications, cognitive behavioural therapy (CBT), exposure and response prevention (ERP) therapy, magnetic seizure therapy, and repetitive transcranial magnetic stimulation (rTMS). However, their OCD symptoms did not improve after exhausting these treatment options, leading them to consider MRgFUS neurosurgery. Participants also commented on the long time that it took to get a referral for MRgFUS neurosurgery and the difficulty to find treatment.

I explored all the traditional medication combos that are used to treat OCD, including the gold-standard heavy hitters like clomipramine, but that was not making a meaningful difference.

I tried CBT, ERP, mindfulness practices with different psychologists, and rTMS … CBT hasn't really worked for me.

I tried magnetic seizure therapy. It was still experimental at the time. And I remember I did that a couple times before, but I stopped because I had a bad experience.

The wait times were extremely long to even get an initial appointment [for MRgFUS neurosurgery].

It was difficult to get treatment for my son because he's a case that seems to be somewhat unique [treatment-resistant OCD] compared to the general OCD population.

MRgFUS Neurosurgery

Awareness About MRgFUS Neurosurgery

Participants highlighted the lack of awareness about MRgFUS neurosurgery as a treatment option for treatment-refractory OCD. Most participants mentioned that they found out about MRgFUS neurosurgery through research or word of mouth. They noted having to self-advocate to get a referral to the MRgFUS program.

I think not a lot of people know about it [MRgFUS neurosurgery] and that it's even an option. For people with treatment-resistant OCD who are not getting relief from medication, it can be really life-saving treatment.

I heard about FUS [MRgFUS] actually from a friend. I was an inpatient with them, so they suffer as well with OCD. I heard from them about the treatment because I reached out to them.

I was researching about the OCD program, I found something called focused ultrasound, and I also read about patient stories online … They [patients treated with MRgFUS] have gotten better. So, when I went to [the hospital], I mentioned the focused ultrasound to the psychiatrist I was seeing.

I asked his [my son's] psychiatrist to look into neurosurgery, which is where we found the FUS clinical trial. So, it was over a year we were trying to access that treatment and finally got it this past June.

Another participant mentioned hesitating to undergo MRgFUS neurosurgery due to the unfamiliarity of neurosurgery as a treatment option for a psychiatric condition like OCD.

It seemed a bit daunting at first. It seemed kind of scary. It wasn't something that I immediately said, "Oh, I need this," because I was thinking, "Oh my gosh, surgery for a mental health condition. That seems a bit far-fetched."

Decision-Making for MRgFUS Neurosurgery

Participants were motivated to seek neurosurgical treatment for their OCD after exhausting most of the traditional treatment options. They reported feeling desperate to find a relief from their condition and considered MRgFUS neurosurgery as their last resort.

We have explored almost every option that we can possibly think of or researched.

The reason I reached out to [the hospital] [to get MRgFUS neurosurgery] is because I was very desperate to find a solution.

I want to do absolutely everything I can to get my neurons in order … even if the focused ultrasound fails, I'm willing to go in for deep brain stimulation.

One participant mentioned that testimonies from people who had positive experiences with MRgFUS neurosurgery motivated them to seek treatment.

Another thing that really propelled me to undergo focused ultrasound is the people who have undergone it said that they've seen progress, and it's helped them. So, I told myself that I'll never know if I will get any benefit from it if I don't undergo this procedure.

Experience With MRgFUS Neurosurgery

Most participants who underwent MRgFUS neurosurgery reported having a positive experience with little to no side effects and a short recovery time.

I would say it's [the surgery experience is] pretty positive. I didn't have any side effects from it. They said your head [was] supposed to hurt for a few days. I didn't have that.

Surgery was fine. There were no side effects from it. It was just a day surgery, and I slept overnight at the hospital. It was fairly painless, except for just a few moments during which there was some pain but tolerable.

Patients reported having to take time off from work for recovery after surgery.

He was working at the time. So, he took time off work. The recommendation from the doctor was a week to 2 weeks postsurgery, depending on the headaches.

I was able to get to work right away; they told me to take a few days off, so I just worked like 2 days after.

Participants who were on the waitlist for MRgFUS neurosurgery mentioned that they felt hopeful waiting for their surgery and viewed it as a last resort. Some participants reported feeling nervous and scared thinking about their upcoming surgery.

The focused ultrasound has been my lifeline mentally. It gives me some hope.

I honestly don't know where we go from here. It's a place you get to at the end of the line, and by the end, you've exhausted your financial resources.

I'm also a little bit nervous about having a brain surgery because it's my first time and I'm afraid something might be wrong.

I'm also worried if the surgery itself will be painful, even though I know that they will be basically turning off my brain.

Impact of MRgFUS Neurosurgery

OCD Symptoms

Participants who underwent MRgFUS neurosurgery reported the impact it had on their OCD symptoms. The effectiveness of MRgFUS neurosurgery varied from patient to patient, but most participants described a lessening of their OCD symptoms following surgery.

That horrible kind of loud, intrusive, constant loops that were playing in my head gradually subsided.

Immediately after the surgery, like for a few months after, his compulsion seemed to lessen.

My OCD symptoms have been really minimal and nonexistent and not impacting my day-to-day life.

However, some participants who underwent MRgFUS neurosurgery have not yet seen positive changes in their OCD symptoms and expressed disappointment.

There was no impact aside from the 3 or 4 good days. It's now 2 months … but it's very disheartening.

Unfortunately, she hasn't got better from it. But I understand it's supposed to take some time before it kicks in.

Mental Health

Participants also reported an improvement in their mental health following MRgFUS neurosurgery. Some mentioned that their depression and anxiety symptoms lessened, while others noted improvement in their sleep.

After surgery, he definitely had improved mood.

It is kind of like a factory reset in terms of his depressive thoughts.

There's a bit of a diminishing in anxiety and depression.

I do notice that my sleep is a bit better. Before, I had a lot of trouble sleeping and relaxing to go to sleep.

Concurrent Treatments

Many participants mentioned that following MRgFUS neurosurgery, they had lowered their dosage of certain medications that are used to treat their OCD or associated depression and anxiety, or stopped taking these medications altogether. Others reported that the lessening of their OCD symptoms after surgery allowed them to have effective therapy sessions.

The goal is eventually to eliminate lorazepam. And we've been doing that successfully so far.

We did reduce one of his medications, so he's no longer on risperidone; his psychologist ended his sessions.

I was able to lower some of it [medication], and I was able to actually come off one of them.

I'm able to do exposure therapy much better than I could before because before I was so anxious about doing exposures, but I would say it's much better now.

Quality of Life

Participants highlighted the positive impact that MRgFUS neurosurgery had on their quality of life. They emphasized the importance of regaining their independence to perform day-to-day activities with little to no support needed from care partners. Some participants mentioned that they were able to go back to school or work following their treatment.

While I was so ill, my parents were taking care of me as a dependent, but after treatment, I was able to get on my own feet and become an independent functioning adult.

I don't have problems with doing activities of daily living like cooking. And [I] can shower and stuff because it doesn't take me as long to do so. I have better social relationships. I'm not disappearing from tasks and people. I do extracurricular activities as well.

I was doing full-time co-op for school and I'm doing school at the same time, so I'm balancing a part-time job as well as school. I'm pretty good for the most part right now.

I was able to start work, so I started teaching at a private school, and then I went back to school, which is what I'm doing now.

Participants also reported that MRgFUS neurosurgery was a life-saving treatment for them at the end of their treatment journey and emphasized the importance of having access to MRgFUS neurosurgery for treatment-refractory OCD.

I had the procedure, and it really saved my life and transformed my life.

It really saved my life and turned my life around.

I would want to emphasize that when we were looking for treatment for our son, if this surgery wasn't available, we would have hit the end of the road.

For some people who are drug-resistant, this might be literally their last option, so I just feel it's very important to have these options open.

Barriers

Participants spoke about the barriers that they faced while trying to access treatment for OCD. They highlighted transportation, cost of treatment, and difficulty navigating the health care system as the main barriers.

Transportation

Because the MRgFUS neurosurgery centre is in a hospital in Toronto, patients who live outside the Greater Toronto Area had to travel long distances to their appointments. Participants reported travelling from other cities in Ontario, as well as out of province, to access treatment. Additionally, some patients travelled with their care partners and had to seek accommodation in a hotel or with relatives near Toronto.

I had to commute from [another city] to Toronto. My mom drove me, and she stayed at a hotel while I had to stay overnight out of hospital posttreatment.

We travelled to Toronto from [another province] for that appointment. We stayed in a hotel for 2 nights and then we were fortunate enough to have family who lived just 2 hours outside of Toronto, so we stayed with them.

I think one of the biggest obstacles for me is that I need someone's help in order to get to the hospital. And thankfully, I always had my dad who drove me to the hospital in Toronto.

Cost of Treatment

Participants reported the financial burden that they faced while paying out of pocket for their OCD treatment, including medication and therapy costs. Since most patients were not able to work and generate income, care partners had to share the financial burden.

> *The cost of his medication has been a lot … and there's the cost for his therapy which is $250 every time he goes. He used to go 3 times a month, but now just to save money, he's going once a month.*

> *We flew home the day after his surgery, and we've had 1 trip for [a] follow-up appointment so far. So that's another 2 nights – the hotel and round-trip plane tickets. So, it's been costly, but worth it.*

> *I was doing therapy for a bit, but I don't think it helped enough and it's too big of an expense to pay out of pocket.*

Challenges in Navigating the Health Care System

Participants reported that they had difficulty finding the right treatment for their condition. They mentioned that after exhausting multiple treatment options for their OCD, getting a referral to the MRgFUS program was a challenge and required a lot of self-advocacy. One participant noted the long wait time to get an initial appointment for MRgFUS neurosurgery.

> *I think the biggest barrier was finding the treatment. Getting him to surgery was a bit of an effort and a push. It wasn't like we went to a doctor and then he said, "Oh, here's your referral," and then you move along the process – we had to navigate the health care system a lot ourselves.*

> *If we didn't ask certain questions or reach out to certain contacts at [the hospital], I don't know if this ever would have happened. So, it was just less organic in receiving the treatment.*

> *The wait times were extremely long to even get an initial appointment. That's something that was difficult to navigate just because of how severe my symptoms were and how desperate I was for some relief.*

Some participants who underwent MRgFUS neurosurgery reported that they felt a lack of support from their health care team following surgery.

> *They didn't help me navigate the system in finding someone [psychiatrist] to see … maybe that's why 6 months after surgery, I had a flare-up in my OCD symptoms.*

> *I think after the surgery, I felt like I was on my own in terms of finding a regular psychiatrist I could see. They said after the surgery, it is important to maintain a regimen of therapy.*

> *There were some barriers because the psychiatrist that I was seeing … doesn't specialize in OCD, so he was limited in terms of medications that he could suggest.*

Preferences and Values Evidence Discussion

All participants had lived experience of OCD or were a family member or care partner of someone with OCD. Participants reported the negative impacts that OCD had on their day-to-day activities, work and school, social life and family relationships, and mental health. They spoke about the journey to manage their condition, the various treatment options that they had explored, and their experience with MRgFUS neurosurgery. Most participants had undergone MRgFUS neurosurgery, while some were on the waitlist to undergo this procedure. Participants also highlighted the importance of expanding access to neurosurgical treatment options such as MRgFUS neurosurgery for people with treatment-refractory OCD.

Our analysis was limited by a lack of geographic representation among participants, most of whom lived in southern Ontario; however, both urban and rural perspectives were provided, and 1 out-of-province participant was included.

Preferences and Values Evidence Conclusions

Participants spoke about the impact of living with OCD. They reflected on their experience undergoing MRgFUS neurosurgery. Most participants who underwent MRgFUS neurosurgery commented on the positive impact that it had on their OCD symptoms, mental health, and quality of life. Those who were on the waitlist expressed their hopeful desire to get relief from their condition following surgery. All patients and care partners emphasized the importance of having access to MRgFUS neurosurgery as a treatment option for treatment-refractory OCD. They regarded MRgFUS neurosurgery as a last resort after exhausting multiple treatment options.

Conclusions of the Health Technology Assessment

Based on 2 small case series, the evidence suggests that MRgFUS neurosurgery for severe, treatment-refractory OCD may improve OCD symptoms, quality of life, and patient functioning, and lead to treatment response for many but not all patients. MRgFUS neurosurgery was also found to have a favourable safety profile. In a minority of cases, the procedure could not be successfully performed owing to skull factors, and no cases of re-treatment were reported. However, the evidence is very uncertain due mainly to limitations in study design, sample size, and statistical power.

The cost-effectiveness of MRgFUS neurosurgery is unknown. There are no directly applicable published data on cost-effectiveness. Due to the lack of comparative clinical evidence, we did not conduct a primary economic evaluation. We estimate that the budget impact of publicly funding MRgFUS neurosurgery for people with treatment-refractory OCD in Ontario would be an additional $1.9 million over 5 years.

Most patients who underwent MRgFUS neurosurgery commented on the positive impact that it had on their OCD symptoms, mental health, and quality of life. All patients and care partners emphasized the importance of having access to MRgFUS neurosurgery as a treatment option for treatment-refractory OCD.

Abbreviations

ALIC: anterior limb of the internal capsule

BVMT-R: Brief Visuospatial Memory Test – Revised

CBT: cognitive behavioural therapy

CCI: Canadian Classification of Health Interventions

CGI: Clinical Global Impression

CGI–I: Clinical Global Impression – Improvement

CGI–S: Clinical Global Impression – Severity

CIHI: Canadian Institute for Health Information

COWAT: Controlled Oral Word Association Test

CT: computed tomography

CVLT-II: California Verbal Learning Test, second edition

DBS: deep brain stimulation

D-KEFS: Delis–Kaplan Executive Function System

dTMS: deep transcranial magnetic stimulation

ERP: exposure and response prevention

FDA: Food and Drug Administration (US)

FrSBe: Frontal Systems Behavior Scale

GAF: Global Assessment of Functioning

GRADE: Grading of Recommendations Assessment, Development, and Evaluation

HDE: Humanitarian Device Exemption

ICD-10-CA: International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada

ICER: incremental cost-effectiveness ratio

IGT: Iowa Gambling Task

K-WAIS: Wechsler Adult Intelligence Scale, Korean version

MRgFUS: magnetic resonance-guided focused ultrasound

MRI: magnetic resonance imaging

NHS EED: National Health Service Economic Evaluation Database

NICE: National Institute for Health and Care Excellence

OCD: obsessive–compulsive disorder

ODB: Ontario Drug Benefit

ODSP: Ontario Disability Support Program

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

QALY: quality-adjusted life-year

RFA: radiofrequency ablation

rTMS: repetitive transcranial magnetic stimulation

SD: standard deviation

SDMT: Symbol Digit Modalities Test

SSRI: selective serotonin reuptake inhibitor

TMS: transcranial magnetic stimulation

WTAR: Wechsler Test of Adult Reading

Y–BOCS: Yale–Brown Obsessive–Compulsive Scale

Glossary

Adverse effect: An adverse effect (or adverse reaction) is an undesired harmful or noxious effect resulting from a preventive, diagnostic, or therapeutic procedure.[135]

Adverse event: An adverse event is an undesired harmful or noxious event temporally associated with a preventive, diagnostic, or therapeutic procedure that may present during or after, but is not necessarily causally related.[135]

Base case: In economic evaluations, the base case is the "best guess" scenario, including any assumptions, considered most likely to be accurate. In health technology assessments conducted by Ontario Health, the reference case is used as the base case.

Budget impact analysis: A budget impact analysis estimates the financial impact of adopting a new health care intervention on the current budget (i.e., the affordability of the new intervention). It is based on predictions of how changes in the intervention mix will impact the level of health care spending for a specific population. Budget impact analyses are typically conducted for a short-term period (e.g., 5 years). The budget impact, sometimes referred to as the net budget impact, is the estimated cost difference between the current scenario (i.e., the anticipated amount of spending for a specific population without using the new intervention) and the new scenario (i.e., the anticipated amount of spending for a specific population following the introduction of the new intervention).

CE mark: A CE (Conformité Européenne) mark is a requirement for medical devices to be marketed and sold in Europe.[136] A CE mark reflects that the device complies with all legally mandated essential requirements.

Cost-effective: A health care intervention is considered cost-effective when it provides additional benefits, compared with relevant alternatives, at an additional cost that is acceptable to a decision-maker based on the maximum willingness-to-pay value.

Cost-effectiveness analysis: Used broadly, "cost-effectiveness analysis" may refer to an economic evaluation used to compare the benefits of 2 or more health care interventions with their costs. It may encompass several types of analysis (e.g., cost-effectiveness analysis, cost–utility analysis). Used more specifically, "cost-effectiveness analysis" may refer to a type of economic evaluation in which the main outcome measure is the incremental cost per natural unit of health (e.g., life-year, symptom-free day) gained.

Cost–utility analysis: A cost–utility analysis is a type of economic evaluation used to compare the benefits of 2 or more health care interventions with their costs. The benefits are measured using quality-adjusted life-years, which capture both the quality and quantity of life. In a cost–utility analysis, the main outcome measure is the incremental cost per quality-adjusted life-year gained.

Decision tree: A decision tree is a type of economic model used to assess the costs and benefits of 2 or more alternative health care interventions. Each intervention may be associated with different outcomes, which are represented by distinct branches in the tree. Each outcome may have a different probability of occurring and may lead to different costs and benefits.

Deterministic sensitivity analysis: Deterministic sensitivity analysis is an approach used to explore uncertainty in the results of an economic evaluation by varying parameter values to observe the potential impact on the cost-effectiveness of the health care intervention of interest. One-way sensitivity analysis accounts for uncertainty in parameter values one at a time, whereas multiway sensitivity analysis accounts for uncertainty in a combination of parameter values simultaneously.

Discounting: Discounting is a method used in economic evaluations to adjust for the differential timing of the costs incurred and the benefits generated by a health care intervention over time. Discounting reflects the concept of positive time preference, whereby future costs and benefits are reduced to reflect their present value. The health technology assessments conducted by Ontario Health use an annual discount rate of 1.5% for both future costs and future benefits.

Equity: Unlike the notion of equality, equity is not about treating everyone the same way.[137] It denotes fairness and justice in process and in results. Equitable outcomes often require differential treatment and resource redistribution to achieve a level playing field among all individuals and communities. This requires recognizing and addressing barriers to opportunities for all to thrive in our society.

Exposure and response prevention (ERP): Exposure and response prevention (ERP) is an effective type of therapy specifically for people with OCD.[138] It is a type of cognitive behavioural therapy.

Health inequity: Health inequities are avoidable inequalities in health between groups of people within countries and between countries.[139] These inequities arise from inequalities within and between societies. Social and economic conditions and their effects on people's lives determine their risk of illness and the actions taken to prevent them becoming ill or treat illness when it occurs.

Humanitarian Device Exemption (HDE): A Humanitarian Device Exemption (HDE) is a specific type of marketing approval from the US Food and Drug Administration (FDA) for a medical device intended for small patient populations.[140] This type of approval is exempt from certain effectiveness requirements and subject to certain profit and use restrictions.

Incremental cost: The incremental cost is the additional cost, typically per person, of a health care intervention versus a comparator.

Incremental cost-effectiveness ratio (ICER): The incremental cost-effectiveness ratio (ICER) is a summary measure that indicates, for a given health care intervention, how much more a health care consumer must pay to get an additional unit of benefit relative to an alternative intervention. It is obtained by dividing the incremental cost by the incremental effectiveness. Incremental cost-effectiveness ratios are typically presented as the cost per life-year gained or the cost per quality-adjusted life-year gained.

Ministry of Health perspective: The perspective adopted in economic evaluations determines the types of costs and health benefits to include. Ontario Health develops health technology assessment reports from the perspective of the Ontario Ministry of Health. This perspective includes all costs and health benefits attributable to the Ministry of Health, such as treatment costs (e.g., drugs, administration, monitoring, hospital stays) and costs associated with managing adverse events caused by treatments. This perspective does not include out-of-pocket costs incurred by patients related to obtaining care (e.g., transportation) or loss of productivity (e.g., absenteeism).

Multiway sensitivity analysis: A multiway sensitivity analysis is used to explore uncertainty in the results of an economic evaluation. It is done by varying a combination of model input (i.e., parameter) values simultaneously between plausible extremes to observe the potential impact on the cost-effectiveness of the health care intervention of interest.

One-way sensitivity analysis: A one-way sensitivity analysis is used to explore uncertainty in the results of an economic evaluation. It is done by varying 1 model input (i.e., a parameter) at a time between its minimum and maximum values to observe the potential impact on the cost-effectiveness of the health care intervention of interest.

Probabilistic analysis: A probabilistic analysis (also known as a probabilistic sensitivity analysis) is used in economic models to explore uncertainty in several parameters simultaneously and is done using Monte Carlo simulation. Model inputs are defined as a distribution of possible values. In each iteration, model inputs are obtained by randomly sampling from each distribution, and a single estimate of cost and effectiveness is generated. This process is repeated many times (e.g., 10,000 times) to estimate the number of times (i.e., the probability) that the health care intervention of interest is cost-effective.

Quality-adjusted life-year (QALY): The quality-adjusted life-year (QALY) is a generic health outcome measure commonly used in cost–utility analyses to reflect the quantity and quality of life-years lived. The life-years lived are adjusted for quality of life using individual or societal preferences (i.e., utility values) for being in a particular health state. One year of perfect health is represented by 1 quality-adjusted life-year.

Reference case: The reference case is a preferred set of methods and principles that provide the guidelines for economic evaluations. Its purpose is to standardize the approach of conducting and reporting economic evaluations, so that results can be compared across studies.

(Treatment) Refractory: Denotes that a person has no or inadequate improvement in their condition with many other trials and combinations of the best available treatment. Refractory OCD can occur at any severity; however, neurosurgery is reserved for people who have severe illness, owing to the profound disabling nature of the condition.

Scenario analysis: A scenario analysis is used to explore uncertainty in the results of an economic evaluation. It is done by observing the potential impact of different scenarios on the cost-effectiveness of a health care intervention. Scenario analyses include varying structural assumptions from the reference case.

Sensitivity analysis: Every economic evaluation contains some degree of uncertainty, and results can vary depending on the values taken by key parameters and the assumptions made. Sensitivity analysis allows these factors to be varied and shows the impact of these variations on the results of the evaluation. There are various types of sensitivity analysis, including deterministic, probabilistic, and scenario.

Societal perspective: The perspective adopted in an economic evaluation determines the types of costs and health benefits to include. The societal perspective reflects the broader economy and is the aggregation of all perspectives (e.g., health care payer and patient perspectives). It considers the full effect of a health condition on society, including all costs (regardless of who pays) and all benefits (regardless of who benefits).

Threshold analysis: A variant on deterministic sensitivity analysis, which involves changing the value of 1 or more parameters until the output of interest crosses some threshold that is considered to have decision relevance.

Time horizon: In economic evaluations, the time horizon is the time frame over which costs and benefits are examined and calculated. The relevant time horizon is chosen based on the nature of the disease and health care intervention being assessed, as well as the purpose of the analysis. For instance, a lifetime horizon would be chosen to capture the long-term health and cost consequences over a patient's lifetime.

Utility: A utility is a value that represents a person's preference for various health states. Typically, utility values are anchored at 0 (death) and 1 (perfect health). In some scoring systems, a negative utility value indicates a state of health valued as being worse than death. Utility values can be aggregated over time to derive quality-adjusted life-years, a common outcome measure in economic evaluations.

Willingness-to-pay value: A willingness-to-pay value is the monetary value a health care consumer is willing to pay for added health benefits. When conducting a cost–utility analysis, the willingness-to-pay value represents the cost a consumer is willing to pay for an additional quality-adjusted life-year. If the incremental cost-effectiveness ratio is less than the willingness-to-pay value, the health care intervention of interest is considered cost-effective. If the incremental cost-effectiveness ratio is more than the willingness-to-pay value, the intervention is considered not to be cost-effective.

Appendices

Appendix 1: International Regulatory Status of the Exablate Neuro

Table A1: International Regulatory Status of the Exablate Neuro MRgFUS System

Jurisdiction(s)	Intended use(s)	Additional information about intended use(s)
Canada,[a] Singapore	• Essential tremor	• Unilateral thalamotomy • Patients must be at least 22 years old • The ventralis intermedius must be identified and accessible for targeted thermal ablation
Argentina, Australia, Brazil, Chile, EU, India, Israel, Kazakhstan, Philippines, Thailand	• Essential tremor • Tremor-dominant idiopathic Parkinson's disease • Neuropathic pain	• Targets in thalamus, subthalamus, and pallidum regions of the brain
South Korea	• Essential tremor • Tremor-dominant idiopathic Parkinson's disease • Neuropathic pain	• Treat movement, pain, and behavioural disorders by thermally ablating normal brain tissue of the basal ganglia and cerebral limbic system
China	• Essential tremor • Tremor-dominant idiopathic Parkinson's disease	• Unilateral thalamotomy • Patients must be at least 22 years old • The ventralis intermedius must be identified and accessible for targeted thermal ablation
Japan	• Essential tremor • Tremor-dominant idiopathic Parkinson's disease • Motor symptoms of Parkinson's disease	• The target is the thalamus for tremor symptoms of Parkinson's disease or essential tremor in cases that are medication resistant • The target is the globus pallidus internal segment for Parkinson's disease in cases that are medication resistant and patients who are not candidates for DBS
Russia	• Essential tremor • Parkinson's disease • Neuropathic pain • Cancerous tumours • Multiple myeloma	• Unilateral treatment for motor disorders and neuropathic pain • Palliative treatment of cancerous tumours • Local tumour control for multiple myeloma
Taiwan	• Essential tremor	• Can be used for the treatment of essential tremor in the brain by heat-induced focusing using ultrasound energy under full MR planning and thermal imaging control
US (FDA)	• Essential tremor • Tremor-dominant idiopathic Parkinson's disease • Motor symptoms of Parkinson's disease	• Unilateral thalamotomy treatment of idiopathic essential tremor patients with medication-refractory tremor and staged by ≥9 mo from the first thalamotomy; patients must be at least 22 years old • The ventralis intermedius must be identified and accessible for targeted thermal ablation • Unilateral thalamotomy (ventralis intermedius) for tremor-dominant Parkinson's disease with medication-refractory tremor; patients must be at least 30 years old • Unilateral pallidotomy of patients with advanced, idiopathic Parkinson's disease with medication-refractory moderate-to-severe motor complications as an adjunct to Parkinson's disease medication treatment; patients must be at least 30 years old; the globus pallidus internus must be identified and accessible for targeted thermal ablation

Abbreviations: DBS, deep brain stimulation; FDA, Food and Drug Administration; MR, magnetic resonance.

[a]Same information for Canadian regulatory status received from Health Canada (email communication, August 2022).

Source: Insightec Regulatory Approvals[44] as of 5 July 2023.

Appendix 2: Literature Search Strategies

Clinical Evidence Search

Search date: August 14, 2023

Databases searched: Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, NHS Economic Evaluation Database, APA PsycInfo

Database segments: EBM Reviews – Cochrane Central Register of Controlled Trials <July 2023>, EBM Reviews – Cochrane Database of Systematic Reviews <2005 to August 9, 2023>, EBM Reviews – NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2023 Week 32>, Ovid MEDLINE(R) ALL <1946 to August 11, 2023>, APA PsycInfo <1967 to August Week 1 2023>

Search Strategy:

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1 exp Obsessive-Compulsive Disorder/ (83745)
2 (anankastic personalit* or (compulsi* adj3 (neuros#s or obsessi* or personalit*)) or hoarding* or (obsessive adj3 (disorder* or neuros#s or personalit*)) or OCD or OCPD or trOCD).ti,ab,kf. (89840)
3 or/1-2 (117135)
4 Magnetic Resonance Imaging, Interventional/ (4086)
5 Ultrasonography, Interventional/ (36631)
6 Ultrasonic Therapy/ (19833)
7 High-Intensity Focused Ultrasound Ablation/ (7043)
8 (((focus* adj3 (ultrasound* or ultra sound* or ultrasonograph* or ultra sonograph*)) or FUS) and (MRI or MR or MRI-guide* or MR-guide* or magnet* resonance* or high-frequenc* or high-intensit*)).ti,ab,kf. (14915)
9 (MR?gFU* or MR?g-FU* or MR?gHIFU* or MR?-HIFU*).ti,ab,kf. (2708)
10 (insightec* or exablate*).ti,ab,kf. (396)
11 (phased array* or (piezoceramic* adj3 (helmet* or transducer*)) or (transducer adj3 helmet*)).ti,ab,kf. (7573)
12 Neurosurgical Procedures/ or Psychosurgery/ or Neurosurgery/ or Ablation Techniques/ (159399)
13 (neuro* surg* or neurosurg* or psychiatric surg* or psycho* surg* or psychosurg* or ablat* or capsulotom* or cingulotom* or leukotom* or tractotom*).ti,ab,kf. (547408)
14 or/12-13 (621820)
15 Magnetic Resonance Imaging/ or Ultrasonography/ (1586646)
16 (magnet* resonance* or mri or mri-guide* or mr-guide* or ultrasound* or ultrasonograph* or high-frequency or high-intensity).ti,ab,kf. (2885348)
17 or/15-16 (3494536)
18 14 and 17 (95746)
19 or/4-11,18 (167031)
20 3 and 19 (577)
21 exp Animals/ not Humans/ (16694649)
22 20 not 21 (488)
23 limit 22 to english language [Limit not valid in CDSR; records were retained] (469)
24 limit 23 to yr="2013 -Current" (283)
25 24 use medall,coch,cctr,cleed (104)
26 exp obsessive compulsive disorder/ (83745)

27 (anankastic personalit* or (compulsi* adj3 (neuros#s or obsessi* or personalit*)) or hoarding* or (obsessive adj3 (disorder* or neuros#s or personalit*)) or OCD or OCPD or trOCD).tw,kw,kf. (91482)
28 or/26-27 (118412)
29 interventional magnetic resonance imaging/ (4047)
30 interventional ultrasonography/ (33979)
31 exp ultrasound therapy/ (38296)
32 (((focus* adj3 (ultrasound* or ultra sound* or ultrasonograph* or ultra sonograph*)) or FUS) and (MRI or MR or MRI-guide* or MR-guide* or magnet* resonance* or high-frequenc* or high-intensit*)).tw,kw,kf,dv. (14988)
33 (MR?gFU* or MR?g-FU* or MR?gHIFU* or MR?-HIFU*).tw,kw,kf,dv. (2722)
34 (insightec* or exablate*).tw,kw,kf,dv. (667)
35 (phased array* or (piezoceramic* adj3 (helmet* or transducer*)) or (transducer adj3 helmet*)).tw,kw,kf,dv. (7604)
36 neurosurgery/ or psychosurgery/ or ablation therapy/ or capsulotomy/ or tractotomy/ (127807)
37 (neuro* surg* or neurosurg* or psychiatric surg* or psycho* surg* or psychosurg* or ablat* or capsulotom* or cingulotom* or leukotom* or tractotom*).tw,kw,kf,dv. (549304)
38 or/36-37 (601003)
39 nuclear magnetic resonance imaging/ or ultrasound/ (1199730)
40 (magnet* resonance* or mri or mri-guide* or mr-guide* or ultrasound* or ultrasonograph* or high-frequency or high-intensity).tw,kw,kf,dv. (2901916)
41 or/39-40 (3325924)
42 38 and 41 (90753)
43 or/29-35,42 (168286)
44 28 and 43 (593)
45 (exp animal/ or nonhuman/) not exp human/ (11875088)
46 44 not 45 (582)
47 limit 46 to english language [Limit not valid in CDSR; records were retained] (560)
48 limit 47 to yr="2013 -Current" (372)
49 48 use emez (247)
50 exp obsessive compulsive disorder/ (83745)
51 (anankastic personalit* or (compulsi* adj3 (neuros#s or obsessi* or personalit*)) or hoarding* or (obsessive adj3 (disorder* or neuros#s or personalit*)) or OCD or OCPD or trOCD).ti,ab,id,hw. (104855)
52 or/50-51 (118045)
53 (((focus* adj3 (ultrasound* or ultra sound* or ultrasonograph* or ultra sonograph*)) or FUS) and (MRI or MR or MRI-guide* or MR-guide* or magnet* resonance* or high-frequenc* or high-intensit*)).ti,ab,id,hw. (18380)
54 (MR?gFU* or MR?g-FU* or MR?gHIFU* or MR?-HIFU*).ti,ab,id,hw. (2567)
55 (insightec* or exablate*).ti,ab,id,hw. (449)
56 (phased array* or (piezoceramic* adj3 (helmet* or transducer*)) or (transducer adj3 helmet*)).ti,ab,id,hw. (7425)
57 neurosurgery/ or psychosurgery/ or lesions/ or tractotomy/ (102861)
58 (neuro* surg* or neurosurg* or psychiatric surg* or psycho* surg* or psychosurg* or ablat* or capsulotom* or cingulotom* or leukotom* or tractotom*).ti,ab,id,hw. (643773)
59 or/57-58 (648090)
60 magnetic resonance imaging/ or ultrasound/ (1357492)
61 (magnet* resonance* or mri or mri-guide* or mr-guide* or ultrasound* or ultrasonograph* or high-frequency or high-intensity).ti,ab,id,hw. (4219256)
62 or/60-61 (4219256)

63 59 and 62 (110567)
64 or/53-56,63 (127371)
65 52 and 64 (623)
66 (animal not human).po. (376878)
67 65 not 66 (623)
68 limit 67 to english language [Limit not valid in CDSR; records were retained] (599)
69 limit 68 to yr="2013 -Current" (374)
70 69 use psyb (33)
71 25 or 49 or 70 (384)
72 71 use medall (95)
73 71 use emez (247)
74 71 use cctr (9)
75 71 use coch (0)
76 71 use cleed (0)
77 71 use psyb (33)
78 remove duplicates from 71 (276)

Economic Evidence Search

Search date: August 14, 2023

Databases searched: Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, NHS Economic Evaluation Database, APA PsycInfo

Database segments: EBM Reviews – Cochrane Central Register of Controlled Trials <July 2023>, EBM Reviews – Cochrane Database of Systematic Reviews <2005 to August 9, 2023>, EBM Reviews – NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2023 Week 32>, Ovid MEDLINE(R) ALL <1946 to August 11, 2023>, APA PsycInfo <1967 to August Week 1 2023>

Search Strategy:

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1 exp Obsessive-Compulsive Disorder/ (83745)
2 (anankastic personalit* or (compulsi* adj3 (neuros#s or obsessi* or personalit*)) or hoarding* or (obsessive adj3 (disorder* or neuros#s or personalit*)) or OCD or OCPD or trOCD).ti,ab,kf. (89840)
3 or/1-2 (117135)
4 Magnetic Resonance Imaging, Interventional/ (4086)
5 Ultrasonography, Interventional/ (36631)
6 Ultrasonic Therapy/ (19833)
7 High-Intensity Focused Ultrasound Ablation/ (7043)
8 (((focus* adj3 (ultrasound* or ultra sound* or ultrasonograph* or ultra sonograph*)) or FUS) and (MRI or MR or MRI-guide* or MR-guide* or magnet* resonance* or high-frequenc* or high-intensit*)).ti,ab,kf. (14915)
9 (MR?gFU* or MR?g-FU* or MR?gHIFU* or MR?-HIFU*).ti,ab,kf. (2708)
10 (insightec* or exablate*).ti,ab,kf. (396)
11 (phased array* or (piezoceramic* adj3 (helmet* or transducer*)) or (transducer adj3 helmet*)).ti,ab,kf. (7573)
12 Neurosurgical Procedures/ or Psychosurgery/ or Neurosurgery/ or Ablation Techniques/ (159399)

13 (neuro* surg* or neurosurg* or psychiatric surg* or psycho* surg* or psychosurg* or ablat* or capsulotom* or cingulotom* or leukotom* or tractotom*).ti,ab,kf. (547408)
14 or/12-13 (621820)
15 Magnetic Resonance Imaging/ or Ultrasonography/ (1586646)
16 (magnet* resonance* or mri or mri-guide* or mr-guide* or ultrasound* or ultrasonograph* or high-frequency or high-intensity).ti,ab,kf. (2885348)
17 or/15-16 (3494536)
18 14 and 17 (95746)
19 or/4-11,18 (167031)
20 3 and 19 (577)
21 exp Animals/ not Humans/ (16694649)
22 20 not 21 (488)
23 22 use coch,cleed (0)
24 Economics/ (291937)
25 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (149018)
26 Economic Aspect/ or exp Economic Evaluation/ (554452)
27 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw,kf. (1495945)
28 exp "Cost"/ (691065)
29 (cost or costs or costing or costly).ti. (349448)
30 cost effective*.tw,kw,kf. (479466)
31 (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* or increment*)).ab,kw,kf. (340690)
32 Monte Carlo Method/ (83819)
33 (decision adj1 (tree* or analy* or model*)).tw,kw,kf. (76255)
34 (markov or markow or monte carlo).tw,kw,kf. (192519)
35 Quality-Adjusted Life Years/ (55958)
36 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw,kf. (123229)
37 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw,kf. (225057)
38 or/24-37 (3160071)
39 22 and 38 (13)
40 39 use medall,cctr (4)
41 23 or 40 (4)
42 exp obsessive compulsive disorder/ (83745)
43 (anankastic personalit* or (compulsi* adj3 (neuros#s or obsessi* or personalit*)) or hoarding* or (obsessive adj3 (disorder* or neuros#s or personalit*)) or OCD or OCPD or trOCD).tw,kw,kf. (91482)
44 or/42-43 (118412)
45 interventional magnetic resonance imaging/ (4047)
46 interventional ultrasonography/ (33979)
47 exp ultrasound therapy/ (38296)
48 (((focus* adj3 (ultrasound* or ultra sound* or ultrasonograph* or ultra sonograph*)) or FUS) and (MRI or MR or MRI-guide* or MR-guide* or magnet* resonance* or high-frequenc* or high-intensit*)).tw,kw,kf,dv. (14988)
49 (MR?gFU* or MR?g-FU* or MR?gHIFU* or MR?-HIFU*).tw,kw,kf,dv. (2722)
50 (insightec* or exablate*).tw,kw,kf,dv. (667)
51 (phased array* or (piezoceramic* adj3 (helmet* or transducer*)) or (transducer adj3 helmet*)).tw,kw,kf,dv. (7604)
52 neurosurgery/ or psychosurgery/ or ablation therapy/ or capsulotomy/ or tractotomy/ (127807)

53 (neuro* surg* or neurosurg* or psychiatric surg* or psycho* surg* or psychosurg* or ablat* or capsulotom* or cingulotom* or leukotom* or tractotom*).tw,kw,kf,dv. (549304)
54 or/52-53 (601003)
55 nuclear magnetic resonance imaging/ or ultrasound/ (1199730)
56 (magnet* resonance* or mri or mri-guide* or mr-guide* or ultrasound* or ultrasonograph* or high-frequency or high-intensity).tw,kw,kf,dv. (2901916)
57 or/55-56 (3325924)
58 54 and 57 (90753)
59 or/45-51,58 (168286)
60 44 and 59 (593)
61 (exp animal/ or nonhuman/) not exp human/ (11875088)
62 60 not 61 (582)
63 Economics/ (291937)
64 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (149018)
65 Economic Aspect/ or exp Economic Evaluation/ (554452)
66 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw,kf. (1495945)
67 exp "Cost"/ (691065)
68 (cost or costs or costing or costly).ti. (349448)
69 cost effective*.tw,kw,kf. (479466)
70 (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* or increment*)).ab,kw,kf. (340690)
71 Monte Carlo Method/ (83819)
72 (decision adj1 (tree* or analy* or model*)).tw,kw,kf. (76255)
73 (markov or markow or monte carlo).tw,kw,kf. (192519)
74 Quality-Adjusted Life Years/ (55958)
75 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw,kf. (123229)
76 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw,kf. (225057)
77 or/63-76 (3160071)
78 62 and 77 (15)
79 78 use emez (11)
80 exp obsessive compulsive disorder/ (83745)
81 (anankastic personalit* or (compulsi* adj3 (neuros#s or obsessi* or personalit*)) or hoarding* or (obsessive adj3 (disorder* or neuros#s or personalit*)) or OCD or OCPD or trOCD).ti,ab,id,hw. (104855)
82 or/80-81 (118045)
83 (((focus* adj3 (ultrasound* or ultra sound* or ultrasonograph* or ultra sonograph*)) or FUS) and (MRI or MR or MRI-guide* or MR-guide* or magnet* resonance* or high-frequenc* or high-intensit*)).ti,ab,id,hw. (18380)
84 (MR?gFU* or MR?g-FU* or MR?gHIFU* or MR?-HIFU*).ti,ab,id,hw. (2567)
85 (insightec* or exablate*).ti,ab,id,hw. (449)
86 (phased array* or (piezoceramic* adj3 (helmet* or transducer*)) or (transducer adj3 helmet*)).ti,ab,id,hw. (7425)
87 neurosurgery/ or psychosurgery/ or lesions/ or tractotomy/ (102861)
88 (neuro* surg* or neurosurg* or psychiatric surg* or psycho* surg* or psychosurg* or ablat* or capsulotom* or cingulotom* or leukotom* or tractotom*).ti,ab,id,hw. (643773)
89 or/87-88 (648090)
90 magnetic resonance imaging/ or ultrasound/ (1357492)

91 (magnet* resonance* or mri or mri-guide* or mr-guide* or ultrasound* or ultrasonograph* or high-frequency or high-intensity).ti,ab,id,hw. (4219256)
92 or/90-91 (4219256)
93 89 and 92 (110567)
94 or/83-86,93 (127371)
95 82 and 94 (623)
96 (animal not human).po. (376878)
97 95 not 96 (623)
98 economics/ or economy/ (405741)
99 pharmacoeconomics/ or health care economics/ (237355)
100 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw. (1454271)
101 exp "costs and cost analysis"/ (740078)
102 cost*.ti. (374690)
103 cost effective*.tw. (472203)
104 (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* or increment*)).ab. (321117)
105 markov chains/ (30432)
106 (decision adj1 (tree* or analy* or model*)).tw. (73708)
107 (markov or markow or monte carlo).tw. (186506)
108 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw. (121775)
109 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw. (220768)
110 or/98-109 (3057736)
111 97 and 110 (14)
112 111 use psyb (0)
113 41 or 62 or 112 (583)
114 41 or 79 or 112 (15)
115 limit 114 to english language [Limit not valid in CDSR; records were retained] (14)
116 115 use medall (4)
117 115 use emez (10)
118 115 use cctr (0)
119 115 use coch (0)
120 115 use cleed (0)
121 115 use psyb (0)
122 remove duplicates from 115 (11)

Grey Literature Search

Performed on: August 18–21, 2023

Websites searched: Alberta Health Evidence Reviews, Alberta Health Services, BC Health Technology Assessments, 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, Centre Hospitalier de l'Université de Québec-Université Laval, Health Technology Assessment Database, Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Centers for Medicare & Medicaid Services Technology Assessments, Veterans Affairs Health Services Research and Development, Institute for Clinical and Economic Review, Oregon Health Authority Health Evidence Review Commission, Washington State

Health Care Authority Health Technology Reviews, National Institute for Health and Care Excellence (NICE), National Health Service England, Healthcare Improvement Scotland, Health Technology Wales, Ireland Health Information and Quality Authority Health Technology Assessments, Australian Government Medical Services Advisory Committee, Australian Safety and Efficacy Register of New Interventional Procedures -Surgical (ASERNIP-S), Italian National Agency for Regional Health Services (AGENAS), Belgian Health Care Knowledge Centre, Ludwig Boltzmann Institute for Health Technology Assessment, Swedish Agency for Health Technology Assessment and Assessment of Social Services, Ministry of Health Malaysia Health Technology Assessment Section, Tuft's Cost-Effectiveness Analysis Registry, PROSPERO, EUnetHTA, ClinicalTrials.gov

Keywords used: obsessive, obsession, compulsive, compulsion, mental health, psychiatric, OCD, hoarding, MR-guided, magnetic resonance, ultrasound, MRgFUS, HIFU, ablation, surgery, neurosurgical, neurosurgery, psychosurgery

Clinical results (included in PRISMA): 5
Economic results (included in PRISMA): 6
Ongoing health technology assessments (PROSPERO/EUnetHTA): 1
Ongoing randomized clinical trials (ClinicalTrials.gov): 7

Appendix 3: Critical Appraisal of Clinical Evidence

Table A2: Risk of Bias[a] Among Case Series of MRgFUS Capsulotomy for Treatment-Refractory OCD

Author, year	Inclusion criteria	Measurement of condition	Valid methods to identify condition	Consecutive cases included	Complete inclusion of cases	Demographics reporting	Clinical information reporting	Outcomes or follow-up	Site or clinic reporting	Appropriate statistical analysis
Davidson et al, 2020[72]	Y[b]	Y[c]	Y[d]	U[e]	U[e]	U[f]	Y[g]	Y[h]	U[i]	Y[j]
Kim et al, 2018[79]	Y[b]	Y[c]	Y[d]	Y[k]	U[k]	U[f]	Y[g]	Y[l]	U[i]	Y[m]

Abbreviations: MRgFUS, magnetic resonance-guided focused ultrasound; N, no; OCD, obsessive–compulsive disorder; U, unclear; Y, yes.

[a]Risk of bias was assessed using the Joanna Briggs Institute's Critical Appraisal Checklist for Case Series.[67]

[b]Explicit inclusion and exclusion criteria were defined and published in protocol.

[c]OCD diagnosis was defined according to the *Diagnostic and Statistical Manual of Mental Disorders* (4th edition, DSM-IV, or 5th edition, DSM-V).

[d]Severity of OCD was based on existing definitions of Yale–Brown Obsessive–Compulsive Scale (Y–BOCS) scores, in addition to standard diagnostic criteria.

[e]Patients referred to the centre were assessed to determine whether they met inclusion criteria and, if so, were offered treatment. One patient with OCD was excluded after enrolment but prior to treatment (because they withdrew consent; see Supplementary Figure 2 in the report by Davidson et al[72]).

[f]Age, sex, and time period were reported, but no information about participants' other demographics was provided (e.g., education, geographic region, ethnicity).

[g]Clear reporting of relevant clinical information of the participants.

[h]All participants were followed after the procedure for at least 6 months, some up to 12 months, with symptoms, complications, and adverse events assessed and documented.

[i]Clinical information on population is sufficiently detailed to judge comparability or differences to other researchers' populations. However, there were partial demographic data, which may or may not be sufficient for this purpose.

[j]Nonparametric tests were used for analysis, which is appropriate given the unknown distribution of the data due to small sample size.

[k]Authors state that participants were recruited from a patient pool at the site and assessed for eligibility. Fourteen patients were assessed for eligibility; 2 did not meet inclusion criteria and 1 declined to participate.

[l]All participants were followed after the procedure for 24 months, with symptoms, complications, and adverse events assessed and documented. Participants lost to follow-up were reported clearly.

[m]Analysis was done with a linear mixed model for repeated measures with unstructured covariance matrix, and post hoc analysis included Bonferroni correction for multiple comparisons.

Table A3: GRADE Evidence Profile for the Effect of MRgFUS Capsulotomy for Treatment-Refractory OCD

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
OCD symptoms: Y–BOCS score							
2 (case series)[72,79]	No serious limitations[a]	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected[c]	None	⨁ Very low
OCD symptoms: treatment response							
2 (case series)[72,79]	No serious limitations[a]	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected[c]	None	⨁ Very low
OCD symptoms: CGI scores							
1 (case series)[79]	No serious limitations[a]	None[d]	No serious limitations	Serious limitations (−1)[b]	Undetected[e]	None	⨁ Very low
Adverse events							
2 (case series)[72,79]	No serious limitations[a]	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected[c]	None	⨁ Very low
Neurocognitive changes							
2 (case series)[72,79]	Serious limitations (−1)[f]	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected[c]	None	⨁ Very low
Technical failure							
2 (case series)[72,79]	Serious limitations (−1)[g]	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected[c]	None	⨁ Very low
Follow-up interventions and re-treatment							
2 (case series)[72,79]	No serious limitations[a]	No serious limitations	No serious limitations	No serious limitations[h]	Undetected[c]	None	⨁ Very low
Quality of life							
1 (case series)[72]	No serious limitations[a]	None[d]	No serious limitations	Serious limitations (−1)[b]	Undetected[e]	None	⨁ Very low
Psychosocial and occupational functioning							
1 (case series)[79]	No serious limitations[a]	None[d]	No serious limitations	Serious limitations (−1)[b]	Undetected[e]	None	⨁ Very low

Abbreviations: CGI, Clinical Global Impression; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; MRgFUS, magnetic resonance-guided focused ultrasound; OCD, obsessive–compulsive disorder; Y–BOCS, Yale–Brown Obsessive–Compulsive Scale.

[a]See risk-of-bias assessment in Appendix 3, Table A2.

[b]Very small sample sizes and optimal information size criteria not met; therefore, uncertainty remains in the precision of estimates.

[c]Cannot definitively assess presence or absence of publication bias because the evidence is derived from 2 studies.

[d]Cannot be evaluated, as there is a single study.

[e]Cannot definitively assess presence or absence of publication bias because the evidence is derived from a single study.

[f]Both studies had missing data for 1 or more patients for this outcome.

[g]Two publications of the study (Kim et al[79] and Jung et al[77]) report apparently conflicting information about treatment failures for the same study (i.e., 1 treatment failure versus none).

[h]No re-treatment or subsequent interventions occurred in either study.

Appendix 4: Selected Excluded Studies – Clinical Evidence

For transparency, we provide a list of selected studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary reason for exclusion
Davidson B, Eapen-John D, Mithani K, et al. Lesional psychiatric neurosurgery: meta-analysis of clinical outcomes using a transdiagnostic approach. J Neurol Neurosurg Psychiatry. 2022;93(2):207-15.	Results for OCD and MRgFUS not presented separately (systematic review)
Stieglitz LH, Oertel MF, Accolla EA, et al. Consensus Statement on High-Intensity Focused Ultrasound for Functional Neurosurgery in Switzerland. Front Neurol. 2021;12:722762.	Guideline – no outcomes of interest
Lai Y, Wang T, Zhang C, et al. Effectiveness and safety of neuroablation for severe and treatment-resistant obsessive-compulsive disorder: a systematic review and meta-analysis. J Psychiatry Neurosci. 2020;45(5):356-69.	Outdated, missing most recent studies (systematic review)
Kinfe T, Stadlbauer A, Winder K, Hurlemann R, Buchfelder M. Incisionless MR-guided focused ultrasound: technical considerations and current therapeutic approaches in psychiatric disorders. Expert Rev Neurother. 2020;20(7):687-96.	No information on search dates, key words (systematic review)
Pepper J, Zrinzo L, Hariz M. Anterior capsulotomy for obsessive-compulsive disorder: a review of old and new literature. J Neurosurg. 2020;133(5):1595-604.	Outdated, missing most recent studies (systematic review)
McGovern RA, Sheth SA. Role of the dorsal anterior cingulate cortex in obsessive-compulsive disorder: converging evidence from cognitive neuroscience and psychiatric neurosurgery. J Neurosurg. 2017;126(1):132-47.	No outcomes of interest (systematic review)
Piper RJ, Hughes MA, Moran CM, Kandasamy J. Focused ultrasound as a non-invasive intervention for neurological disease: a review. Br J Neurosurg. 2016;30(3):286-93.	Wrong study type (narrative review)
Davidson B, Hamani C, Rabin JS, et al. Magnetic resonance-guided focused ultrasound capsulotomy for musical obsessions. Biol Psychiatry. 2021;90(10):e49-e50.	Duplicate report (case data included in case series)

Appendix 5: Neuropsychological Tests in Patients With OCD

Table A4: Overview of Neuropsychological Test Results at Baseline and Follow-Up After MRgFUS Capsulotomy in 5 People with Treatment-Refractory OCD

Test	Function(s) measured	Baseline, mean (SD)[a]	6 mo, mean (SD)[a]	12 mo, mean (SD)[a]
Wechsler Test of Adult Reading (WTAR)	Intellectual functioning	103.4 (5.46)	NA[b]	NA[b]
California Verbal Learning Test, second edition (CVLT-II)	Memory – total recall	52.4 (9.45)	53.6 (9.21)	50.6 (10.24)
	Memory – delayed free recall	−0.1 (1.08)	−0.5 (0.87)	0.6 (1.19)
	Memory – delayed cued recall	0.1 (0.65)	0.2 (0.57)	0.4 (0.82)
	Memory – delayed recognition discrimination	0.4 (0.65)	0.3 (0.27)	0.4 (0.65)
Brief Visuospatial Memory Test – Revised (BVMT-R)	Memory – immediate recall	37.4 (15.36)	45.8 (8.44)	47 (15.3)
	Memory – delayed recall	39.6 (15.5)	47.2 (5.76)	50.8 (13.79)
Delis–Kaplan Executive Function System (D-KEFS) sorting test	Executive function – correct sorts	8.8 (1.64)	11 (1)	11.8 (3.27)
	Executive function – descriptive score	9.2 (1.30)	10.8 (1.3)	11 (3.39)
Symbol Digit Modalities Test (SDMT), oral version	Cognitive processing	−1.36 (0.63)	−0.96 (0.31)	−0.9 (0.51)
Iowa Gambling Task (IGT) total score	Cognitive function	44.2 (10.78)	48.67 (11.93)[c]	51 (5.35)[d]
Frontal Systems Behavior Scale (FrSBe), self-report version	Apathy, disinhibition, executive dysfunction – total score	7.8 (17.81)	58 (12.43)	57.6 (16.47)
	Disinhibition score	51.6 (17.60)	47.4 (15.04)	40.8 (8.41)
	Apathy score	80.8 (20.68)	66 (13.55)	65.6 (25.51)
	Dysexecutive score	73 (19.30)	61.4 (8.68)	61.2 (15.90)

Abbreviations: MRgFUS, magnetic resonance-guided focused ultrasound; NA, not assessed; OCD, obsessive–compulsive disorder; SD, standard deviation.

[a]Calculated for patients with OCD from individual patient data from Supplementary Table 2 in the report by Davidson et al.[75]

[b]Assessed only to determine baseline intellectual functioning.

[c]n = 3.

[d]n = 4.

Source: Davidson et al.[75]

Appendix 6: Results of the Applicability Checklist for Studies Included in the Economic Literature Review

Table A5: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of MRgFUS Neurosurgery

Author, year, country	Is the study population similar to the question?	Are the interventions similar to the question?	Is the health care system studied sufficiently similar to Ontario?	Were the perspectives clearly stated? If yes, what were they?	Are all direct effects included? Are all other effects included where they are material?	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of QALYs?	Are costs and outcomes from other sectors fully and appropriately measured and valued?	Overall judgment[a]
Kumar et al, 2019,[94] US	Yes, patients with treatment-refractory OCD	Yes, includes MRgFUS neurosurgery and RFA	Partially	No, stated societal but only hospital costs of procedure and some complications were included	Partially, only treatment effects for the comparator were included	N/A; time horizon, 1 y	Yes	No, only hospital costs were included	Not applicable

Note: Response options for all items were "yes," "partially," "no," "unclear," and "N/A" (not applicable).

Abbreviations: MRgFUS, magnetic resonance-guided focused ultrasound; OCD, obsessive–compulsive disorder; QALY, quality-adjusted life-year; RFA, radiofrequency ablation; Y–BOCS, Yale–Brown Obsessive–Compulsive Scale.

[a]Overall judgment may be "directly applicable," "partially applicable," or "not applicable."

Appendix 7: Supplementary Economic Tables

Table A6: CCI Codes for Intervention and Comparators

Intervention category	CCI code	Long description
MRgFUS neurosurgery	1AE59JAAZ	Destruction, thalamus and basal ganglia using ultrasound, external approach
RFA	1AE59SEGX	Destruction, thalamus and basal ganglia using device NEC, burr hole approach
	1AE59SZAW	Destruction, thalamus and basal ganglia using radiofrequency probe, open approach
	1AE59SZGX	Destruction, thalamus and basal ganglia using device NEC, open approach
	1AE59SEAW	Destruction, thalamus and basal ganglia using radiofrequency probe, burr hole approach
	1AN59SEAW	Destruction, brain with radiofrequency probe, burr hole approach
	1AN59SEGX	Destruction, brain with device NEC, burr hole technique
	1AN59SZAW	Destruction, brain with radiofrequency probe, craniotomy flap technique for access
	1AN59SZGX	Destruction, brain with device NEC, open approach
Gamma Knife radiosurgery	1AE27JX	Radiation, thalamus and basal ganglia using focused beam [e.g., Gamma Knife, CyberKnife stereotactic radiosurgery]
	1AN27JX	Radiation, brain using focused beam [e.g., Gamma Knife, CyberKnife stereotactic radiosurgery]
DBS	1AE53SEJA	Implantation of internal device, thalamus and basal ganglia of electrodes [e.g., recording, stimulating] using burr hole approach
	1AE53SZJA	Implantation of internal device, thalamus and basal ganglia of electrodes [e.g., recording, stimulating] using open approach
	1AN53SEJA	Implantation of internal device, brain of electrodes [e.g., recording, stimulating] using burr hole approach
	1AN53SZJA	Implantation of internal device, brain of electrodes [e.g., recording, stimulating] (craniotomy flap technique for access)

Abbreviations: CCI, Canadian Classification of Health Interventions; DBS, deep brain stimulation; MRgFUS, magnetic resonance-guided focused ultrasound; NEC, not elsewhere classified; RFA, radiofrequency ablation.

Table A7: ICD-10-CA Codes for OCD Diagnoses

ICD-10-CA code	ICD-10-CA description
F420[a]	Predominantly obsessional thoughts or ruminations
F421[a]	Predominantly compulsive acts (obsessional rituals)
F422[a]	Mixed obsessional thoughts and acts
F428	Other obsessive–compulsive disorders
F429	Obsessive–compulsive disorder, unspecified

Abbreviations: ICD-10-CA, International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada; OCD, obsessive–compulsive disorder.

[a]Code was included in search, but no cases were identified.

Table A8: Inpatient Costs

Procedure	CCI codes	Diagnosis code(s)	Years	Number of cases	Mean cost, $[a]	Standard deviation, $[a]	Mean length of stay, d	95% confidence interval, $[a,b]
RFA	1AN59SEAW, 1AN59SEGX	F429	2017–2022	8	4,327	3,677	1.6	1,256–7,420
Gamma Knife radiosurgery	1AE27JX, 1AN27JX	F428, F429	2019–2022	5	1,741	131	1.0	1,583–1,908
DBS	1AE53SEJA, 1AESZJA, 1AN53SEJA	F428, F429	2012–2019	7	27,557	8,792	1.7	NA

Abbreviations: CCI, Canadian Classification of Health Interventions; DBS, deep brain stimulation; NA, not available; RFA, radiofrequency ablation.

[a]All costs are reported in 2023 Canadian dollars.

[b]95% confidence intervals were calculated from the IntelliHealth Ontario data assuming that the data followed a *t*-distribution owing to small sample sizes.

Source: IntelliHealth Ontario, accessed July 5, 2023.

Table A9: Capital and Fixed Costs of MRgFUS Neurosurgery

Resource item	Cost, $[a]
Insightec Exablate Neuro system and equipment	2,370,207
Installation	218,788
Annual depreciation	
Equipment depreciation (Insightec Exablate Neuro)	517,799[b]
Equipment depreciation (head frame)	13,370
Annual service contract (echo focusing system)	60,775
Annual service contract (Insightec Exablate Neuro)	151,936
Total fixed cost per year	**743,880**
Annual caseload	66[c]
Useful life (years)	5
Average fixed cost per case	**11,271**

Note: Numbers may be inexact due to rounding.

[a]All costs are reported in 2023 Canadian dollars.

[b]Insightec equipment and installation cost divided by useful life.

[c]Includes 48 essential tremor cases and an average of 18 OCD cases annually.

Table A10: Surgical Assistant Fees

Procedure	MRgFUS neurosurgery	RFA	Gamma Knife radiosurgery	DBS	Source
Average surgery treatment time, h	3	3	N/A	4.5	Expert opinion[a]
Number of basic units	9	9	N/A	9	Schedule of Benefits[103] (N124)
Number of time units[b]	22	22	N/A	40	Calculated based on average surgery length
Total number of units	31	31	N/A	49	
Unit price, $[c]	12.51	12.51	12.51	12.51	Schedule of Benefits[103] (N124)
Total cost, $[c]	**388**	**388**	**N/A**	**613**	

Abbreviations: DBS, deep brain stimulation; MRgFUS, magnetic resonance-guided focused ultrasound; N/A, not applicable; RFA, radiofrequency ablation.

[a]N. Lipsman, MD, PhD, email communication, December 18, 2023.

[b]Time units are calculated according to rules in the Schedule of Benefits as follows: 1 unit per 15-minute increment in the first hour, 2 units per 15-minute increment after the first hour up to 2.5 hours, and 3 units per 15-minute increment after 2.5 hours.

[c]All costs are reported in 2023 Canadian dollars.

Table A11: Anesthesiologist Fees

Procedure	MRgFUS neurosurgery	RFA	Gamma Knife radiosurgery	DBS	Source
Average surgery treatment time, h	3	3	N/A	4.5	
Number of basic units	11	11	N/A	11	Schedule of Benefits[103] (N124)
Number of time units[a]	26	26	N/A	44	Calculated based on average surgery length
Total number of units	37	37	N/A	55	
Unit price, $[b]	15.49	15.49	N/A	15.49	Schedule of Benefits[103] (N124)
Total cost, $[b]	**573**	**573**	**N/A**	**852**	

Abbreviations: DBS, deep brain stimulation; MRgFUS, magnetic resonance-guided focused ultrasound; N/A, not applicable; RFA, radiofrequency ablation.

[a]Time units are calculated according to rules in the Schedule of Benefits as follows: 1 unit per 15-minute increment in the first hour, 2 units per 15-minute increment after the first hour up to 1.5 hours, and 3 units per 15-minute increment after 1.5 hours.

[b]All costs are reported in 2023 Canadian dollars.

Table A12: Cost of Adjunct Medications

Medication	Daily dose, mg/d	Unit cost, $/mg	Cost per dose, $[a]	Annual cost, $	Source
Patient 1[b]					
Amitriptyline	300	0.0031	0.924	337.26	ODB Formulary[119,c]
Citalopram	40	0.00333	0.1332	48.62	ODB Formulary[119,c]
Risperidone	1.5	1.1176	1.6764	611.89	ODB Formulary[119,c]
Total annual cost				**997.76**	
Patient 2[b]					
Sertraline	250	0.0061	1.5160	553.34	ODB Formulary[119,c]
Risperidone	2	1.1176	2.2352	815.85	ODB Formulary[119,c]
Lorazepam	1	0.0718	0.0718	26.21	ODB Formulary[119,c]
Clonazepam	1.5	0.0836	0.1254	45.77	ODB Formulary[119,c]
Total annual cost				**1,441.17**	
Patient 3[b]					
Paroxetine	40	0.01625	0.65	237.25	ODB Formulary[119,c]
Clonazepam	1	0.0836	0.0836	30.51	ODB Formulary[119,c]
Memantine	10	0	0	0.00	ODB Formulary[119,c]
Total annual cost				**276.76**	
Patient 4[b]					
Clomipramine	300	0.0126	3.7746	1,377.73	ODB Formulary[119,d]
Desvenlafaxine	200	0	0	0.00	ODB Formulary[119,d]
Lurasidone	40	0.030625	1.225	447.13	ODB Formulary[119,d]
Lorazepam	1	0.0718	0.0718	26.21	ODB Formulary[119,c]
Total annual cost				**1,851.06**	
Patient 5[b]					
Nil				0.00	
Total annual cost				**0.00**	
Patient 6[b]					
Fluoxetine	60	0.016555	0.9933	362.55	ODB Formulary[119,d]
Nortriptyline	20	0.02995	0.599	218.64	ODB Formulary[119,d]
Clonazepam	2.25	0.0836	0.1881	68.66	ODB Formulary[119,c]
Trazodone	50	0.001108	0.0554	20.22	ODB Formulary[119,d]
Lorazepam	4	0.0718	0.2872	104.83	ODB Formulary[119,c]
Total annual cost				**774.90**	
Average annual medications costs[e]	**928.78**				

Abbreviation: ODB, Ontario Drug Benefit.

[a]Unit costs represent the cost paid by the ODB Program (Ministry of Health) plus an 8% markup. If the unit cost is $0, none of the cost of the medication is paid for by the ODB Program.

[b]Medications at time of MRgFUS neurosurgery for patients with OCD as reported in Supplementary Table 2 in the report by Davidson et al.[72]

[c]Accessed October 24, 2023.

[d]Accessed November 2, 2023.

[e]Includes $10 dispensing fee, 4 times per year.

Table A13: Volume of Treatments in Selected Scenario Analyses

Scenario	Year 1 (2024)	Year 2 (2025)	Year 3 (2026)	Year 4 (2027)	Year 5 (2028)	Total
Scenario 1, population of interest						
Current scenario						
Gamma Knife radiosurgery	2	2	2	2	2	10
RFA	2	2	2	2	2	10
No surgery (expanded population)	38	39	39	40	41	197
New scenario						
Gamma Knife radiosurgery, 15% of original population	1	1	1	1	1	5
RFA, 0%	0	0	0	0	0	0
MRgFUS neurosurgery, 85% of original population + expansion	41	42	42	43	44	212
Scenario 2, increased expansion of MRgFUS neurosurgery						
Current scenario						
Gamma Knife radiosurgery	2	2	2	2	2	10
RFA	2	2	2	2	2	10
No surgery (expanded population)	12	17	21	26	30	106
New scenario						
Gamma Knife radiosurgery, 15% of original population	1	1	1	1	1	5
RFA, 0%	0	0	0	0	0	0
MRgFUS neurosurgery, 85% of original population + expansion	15	20	24	29	33	121
Scenario 3, steady but slower expansion of MRgFUS neurosurgery						
Current scenario						
Gamma Knife radiosurgery	2	2	2	2	2	10
RFA	2	2	2	2	2	10
No surgery (expanded population)	12	12	12	12	12	60
New scenario						
Gamma Knife radiosurgery, 15% of original population	1	1	1	1	1	5
RFA, 0%	0	0	0	0	0	0
MRgFUS neurosurgery, 85% of original population + expansion	15	15	15	15	15	75
Scenario 4, steady but increased expansion of MRgFUS neurosurgery						
Current scenario						
Gamma Knife radiosurgery	2	2	2	2	2	10
RFA	2	2	2	2	2	10
No surgery (expanded population)	24	24	24	24	24	120
New scenario						
Gamma Knife radiosurgery, 15% of original population	1	1	1	1	1	5
RFA, 0%	0	0	0	0	0	0
MRgFUS neurosurgery, 85% of original population + expansion	27	27	27	27	27	135
Scenario 5, decreased Gamma Knife radiosurgery						
Current scenario						
Gamma Knife radiosurgery	2	2	2	2	2	10

Scenario	Year 1 (2024)	Year 2 (2025)	Year 3 (2026)	Year 4 (2027)	Year 5 (2028)	Total
RFA	2	2	2	2	2	10
No surgery (expanded population)	12	15	18	21	24	90
New scenario						
Gamma Knife radiosurgery, 15% of original population	0	0	0	0	0	0
RFA, 0%	0	0	0	0	0	0
MRgFUS neurosurgery, 85% of original population + expansion	16	19	22	25	28	110
Scenario 6, patients not eligible for MRgFUS neurosurgery receive RFA						
Current scenario						
Gamma Knife radiosurgery	2	2	2	2	2	10
RFA	2	2	2	2	2	10
No surgery (expanded population)	12	15	18	21	24	90
New scenario						
Gamma Knife radiosurgery, 0%	0	0	0	0	0	0
RFA, 15% of original population	1	1	1	1	1	5
MRgFUS neurosurgery, 85% of original population + expansion	15	18	21	24	27	105

Abbreviations: MRgFUS, magnetic resonance-guided focused ultrasound; RFA, radiofrequency ablation.

Table A14: Detailed Budget Impact Analysis Results – Reference Case

Current scenario	Year 1, $[a]	Year 2, $[a]	Year 3, $[a]	Year 4, $[a]	Year 5, $[a]	Total, $[a]
MRgFUS neurosurgery						
Surgical procedure costs	0	0	0	0	0	**0**
Monitoring costs	0	0	0	0	0	**0**
Adjunct medication costs	0	0	0	0	0	**0**
Adverse event costs	0	0	0	0	0	**0**
RFA						
Surgical procedure costs	23,732	23,732	23,732	23,732	23,732	**118,660**
Monitoring costs	445	890	1,335	1,780	2,225	**6,675**
Adjunct medication costs	1,486	2,972	4,458	5,944	7,430	**22,291**
Adverse event costs	577	577	577	577	577	**2,884**
Gamma Knife radiosurgery						
Surgical procedure costs	14,168	14,168	14,168	14,168	14,168	**70,838**
Monitoring costs	445	890	1,335	1,780	2,225	**6,675**
Adjunct medication costs	1,486	2,972	4,458	5,944	7,430	**22,291**
Adverse event costs	2,399	2,399	2,399	2,399	2,399	**11,995**
No (surgical) treatment						
Surgical procedure costs	0	0	0	0	0	**0**
Monitoring costs	0	0	0	0	0	**0**
Adjunct medication costs	8,916	20,062	33,436	49,039	66,872	**178,325**
Adverse event costs	0	0	0	0	0	**0**
Total	**53,654**	**68,661**	**85,898**	**105,363**	**127,058**	**440,634**
New scenario	**Year 1, $[a]**	**Year 2, $[a]**	**Year 3, $[a]**	**Year 4, $[a]**	**Year 5, $[a]**	**Total, $[a]**
MRgFUS neurosurgery						
Surgical procedure costs	281,523	337,827	394,132	450,437	506,741	**1,970,660**
Monitoring costs	3,338	7,343	12,015	17,355	23,363	**63,413**
Adjunct medication costs	11,145	24,520	40,123	57,956	78,017	**211,761**
Adverse event costs	0	0	0	0	0	**0**
RFA						
Surgical procedure costs	0	0	0	0	0	**0**
Monitoring costs	0	0	0	0	0	**0**
Adjunct medication costs	0	0	0	0	0	**0**
Adverse event costs	0	0	0	0	0	**0**
Gamma Knife radiosurgery						
Surgical procedure costs	7,084	7,084	7,084	7,084	7,084	**35,419**
Monitoring costs	223	445	668	890	1,113	**3,338**
Adjunct medication costs	743	1,486	2,229	2,972	3,715	**11,145**
Adverse event costs	1,200	1,200	1,200	1,200	1,200	**5,998**
No (surgical) treatment						
Surgical procedure costs	0	0	0	0	0	**0**
Monitoring costs	0	0	0	0	0	**0**

Adjunct medication costs	0	0	0	0	0	**0**
Adverse event costs	0	0	0	0	0	**0**
Total	**305,255**	**379,904**	**457,450**	**537,893**	**621,232**	**2,301,733**
Budget impact	**Year 1, $[a]**	**Year 2, $[a]**	**Year 3, $[a]**	**Year 4, $[a]**	**Year 5, $[a]**	**Total, $[a]**
MRgFUS neurosurgery						
Surgical procedure costs	281,523	337,827	394,132	450,437	506,741	**1,970,660**
Monitoring costs	3,338	7,343	12,015	17,355	23,363	**63,413**
Adjunct medication costs	11,145	24,520	40,123	57,956	78,017	**211,761**
Adverse event costs	0	0	0	0	0	**0**
RFA						
Surgical procedure costs	−23,732	−23,732	−23,732	−23,732	−23,732	**−118,660**
Monitoring costs	−445	−890	−1,335	−1,780	−2,225	**−6,675**
Adjunct medication costs	−1,486	−2,972	−4,458	−5,944	−7,430	**−22,291**
Adverse event costs	−577	−577	−577	−577	−577	**−2,884**
Gamma Knife radiosurgery						
Surgical procedure costs	−7,084	−7,084	−7,084	−7,084	−7,084	**−35,419**
Monitoring costs	−223	−445	−668	−890	−1,113	**−3,338**
Adjunct medication costs	−743	−1,486	−2,229	−2,972	−3,715	**−11,145**
Adverse event costs	−1,200	−1,200	−1,200	−1,200	−1,200	**−5,998**
No (surgical) treatment						
Surgical procedure costs	0	0	0	0	0	**0**
Monitoring costs	0	0	0	0	0	**0**
Adjunct medication costs	−8,916	−20,062	−33,436	−49,039	−66,872	**−178,325**
Adverse event costs	0	0	0	0	0	**0**
Total	**251,601**	**311,243**	**371,552**	**432,529**	**494,174**	**1,861,100**

Note: Numbers may be inexact due to rounding.

Abbreviations: MRgFUS, magnetic resonance-guided focused ultrasound; RFA, radiofrequency ablation.

[a]All costs are reported in 2023 Canadian dollars.

Appendix 8: Letter of Information

LETTER OF INFORMATION

Ontario Health

Ontario Health is conducting a review of **Magnetic Resonance-Guided Focused Ultrasound Neurosurgery for treatment-refractory Obsessive–Compulsive Disorder.** The purpose is to better understand how this technique can be publicly funded in Ontario.

An important part of this review involves gathering perspectives of patients and caregivers of those who have been diagnosed and/or managed with non-small cell lung cancer and who may or may not have used plasma-based comprehensive genomic profiling.

WHAT DO YOU NEED FROM ME

- ✓ Willingness to share your story
- ✓ 30-40 minutes of your time for a phone interview
- ✓ 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 Ontario Health (OH) staff. OH staff will contact interested participants by collecting contact information (i.e., email address and/or phone number) to set up an interview. The interview will last about 30-40 minutes. It will be held over the telephone. With your permission, the interview will be audio-taped. The interviewer will ask you questions about your or your loved one's condition and your perspectives about your cancer diagnosis and treatment options in Ontario. Participation is voluntary. You may refuse to participate, refuse to answer any questions or withdraw before or at any point during your interview. Withdrawal will in no way affect the care you receive.

CONFIDENTIALITY

All information you share will be kept confidential and your 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 until project completion. After completion of the project, the records will be destroyed. If you are sending us personal information by email, please be aware that electronic communication is not always secure and can be vulnerable to interception.

Ontario Health is designated an "institution" by the *Freedom of Information and Protection of Privacy Act* (FIPPA) and is collecting your personal information pursuant to FIPPA and the *Connecting Care Act, 2019* to support the Health Technology Assessment Program. If you have any questions regarding Ontario Health's collection and use of personal information for the purposes of this program, please contact us as noted below.

RISKS TO PARTICIPATION

There are no known physical risks to participating. Some participants may experience discomfort or anxiety after speaking about their experience.

IF YOU ARE INTERESTED, PLEASE CONTACT US:

Appendix 9: Interview Guide

Interview Guide MRgFUS

Intro
Explain HTA process, and purpose of interview.

Impact of living with OCD

- Can you describe the symptoms of your OCD?
- What is the impact of OCD on your quality of life? (probe: social, emotional, financial, mental health, work, family, day to day)

Care journey

- How did you seek care to manage your OCD?
- Can you describe your diagnosis journey with OCD?
- What treatment options have you explored?
- Were you aware of MRgFUS?
  - How were you referred to MRgFUS?
  - Decision-making: exploration of alternative, stigma around psychosurgery
    - How was your experience with surgery?
      - What arrangements had to be made for you to have the surgery (childcare, transportation, etc.)?
      - Feelings going into surgery?
      - How long did you stay in the hospital?
      - How was your overall experience with the surgery?
      - Were there any barriers to you accessing this surgery?
    - Post-surgery:
      - How was your overall experience post-surgery?
      - How long was your recovery time?
      - Did you have support from the health care team, family members, caregivers? If so, can you describe?

Impact

- Can you comment on any ways in which you believe your mood symptoms (depressive/anxiety/stress/worry) have changed since treatment with MRgFUS/DBS?
- Can you comment on any ways in which you believe your obsessive thoughts have changed since treatment with MRgFUS/DBS?
- What was the impact of this treatment (MRgFUS) on your overall quality of life? (probe: day to day, mental health, social relationships, work)
- Has there been an impact on your previous therapies for OCD (changes in medication, talk therapy, etc.)?

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About Us

We are an agency created by the Government of Ontario to connect, coordinate, and modernize our province's health care system. We work with partners, providers, and patients to make the health system more efficient so everyone in Ontario has an opportunity for better health and well-being.

Equity, Inclusion, Diversity and Anti-Racism

Ontario Health is committed to advancing equity, inclusion and diversity and addressing racism in the health care system. As part of this work, Ontario Health has developed an Equity, Inclusion, Diversity and Anti-Racism Framework, which builds on existing legislated commitments and relationships and recognizes the need for an intersectional approach.

Unlike the notion of equality, equity is not about sameness of treatment. It denotes fairness and justice in process and in results. Equitable outcomes often require differential treatment and resource redistribution to achieve a level playing field among all individuals and communities. This requires recognizing and addressing barriers to opportunities for all to thrive in our society.

For more information about Ontario Health, visit OntarioHealth.ca.

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