FULL PAPER

The cost-effectiveness of unilateral magnetic resonance-guided focused ultrasound in comparison with unilateral deep brain stimulation for the treatment of medically refractory essential tremor in England

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Objectives: This study aims to ascertain the cost-effectiveness of magnetic resonance-guided focused ultrasound (MRgFUS) for the treatment of medically refractory Essential Tremor (mrET) in England. Essential Tremor (ET) is the most common movement disorder affecting approximately 1 million in the UK causing considerable societal impact affecting patients, carers and the wider healthservice. Medical treatment has mixed efficacy, with approximately 25–55% of ET medication refractory. Deep brain stimulation (DBS) is a proven neurosurgical treatment; however, the risks of surgery and anaesthesia mean some patients are ineligible. MRgFUS is an emerging noninvasive technique that causes tremor suppression by thermal ablation of tremor-sensitive brain tissue. Several international clinical trials have demonstrated MRgFUS is safe and clinically effective; however, to-date no cost-effectiveness study has been performed in Europe.

Methods: A Markov model was used to assess two subpopulations of mrET – those eligible and those ineligible for neurosurgery – in the context specific to England and its healthcare system. For those eligible for neurosurgery, MRgFUS was compared to DBS, the current standard treatment. For those ineligible for neurosurgery, MRgFUS was compared to treatment with medication alone. The model calculated the Incremental cost-effectiveness ratio (ICER) with appropriate sensitivity and scenario analyses.

Results: For those eligible for neurosurgery: In the model base case, the MRgFUS was economically dominant compared to DBS; MRgFUS was less costly (£19,779 vs £62,348) and more effective generating 0.03 additional quality-adjusted life-years (QALYs) per patient (3.71 vs 3.68) over the 5-year time horizon. For those ineligible for neurosurgery: In the model base case, MRgFUS cost over £16,000 per patient more than medication alone (£19,779 vs £62,348) but yielded 0.77 additional QALYs per patient (3.71 vs 2.95), producing an incremental cost-effectiveness ratio (ICER) of £20,851 per QALY. This ICER of £20,851 per QALY falls within the National Institute for Clinical Excellence’s (NICE) willingness to pay threshold (WTP) of 20,000–30,000 demonstrating the cost-effectiveness profile of MRgFUS.

Conclusion: This study demonstrates the favourable cost-effectiveness profile of MRgFUS for the treatment of mrET in England; in both patients suitable and not suitable for neurosurgery.

Advances in knowledge: The introduction of MRgFUS as a widely available ET treatment in UK is currently undergoing the necessary stages of regulatory approval. As the first European study, these favourable cost-effectiveness outcomes (notably the model base case ICER falling within NICE’s WTP) can provide a basis for future commissioning of brain MRgFUS treatments in the UK, Europe and globally.

INTRODUCTION

Essential Tremor (ET) is a progressive neurological disorder characterised by bilateral arm tremor, that can extend to the body.1 Numerous studies have demonstrated the impact of manual impairment on activities of daily living, often leading to disability, social handicap and increased risk
of depression and anxiety. Importantly, tremor in ET occurs in the absence of other progressive neurological processes, e.g. sensory, motor or mood disturbance; this is a key distinction from other conditions which may include tremor such as Parkinson’s disease. As the most prevalent movement disorder worldwide (~7 million in the USA, ~1 million in the UK), the societal impact from ET disability is considerable.

The pathophysiology of ET remains under debate; theories include disordered stimulation of the cerebellum-thalamo-cortical network. Medical treatments including propanol and primidone have mixed efficacy. Patients may trial combination therapy, although many experience waning clinical effectiveness with approximately 25–55% patients medication refractory. Deep Brain Stimulation (DBS), where electrodes connected to a stimulator are implanted deep in the brain, is a proven surgical treatment for ET. However, its clinical effectiveness can wane over time and most patients continue to take tremor medication. DBS patients require regular follow-up for stimulator optimisation and some complications including lead fracture, infection and battery failure can require re-operation.

Magnetic resonance-guided focused ultrasound (MRgFUS) is an emerging technique to treat various neurological conditions including ET. MRgFUS focuses multiple high-energy, low-frequency ultrasound beams on a single tremor-specific site. Heat generated at this site leads to thermal coagulative necrosis of the tremor-specific tissue monitored in real-time by magnetic resonance thermography. This non-invasive technique does not require general anaesthesia, making it suitable for patients ineligible for neurosurgery. As the patient is awake, treatments are tailored to individual neuroanatomy with precision targeting of tremor sensitive tissue, thus sparing non-tremor sensitive tissue, and minimising adverse effects. Several international and national clinical trials have demonstrated MRgFUS a safe and clinically effective treatment for ET.

Depending on individual healthcare systems, commissioning of new treatments and services are required to go through many stages of regulation and approval. In the USA, the first pilot study in 2013 paved the way for FDA approval in 2016 and state-wide Medicare approval in 2020. In the UK, research and private treatments have been performed at Imperial College Healthcare Trust since 2016. National Health Service (NHS) England has now commissioned 150 ET treatments per year at designated centres.

All healthcare systems are required to consider how they allocate scarce resources. For both smaller private providers and large government systems, limited funds need to be allocated for the management of both acute and chronic disease. With persistent competition for funding, many institutions set in place processes, guidelines and minimum evidential requirements before decisions on health policy or funding can be made. In the UK, the National Institute of Clinical Effectiveness (NICE) is instrumental in decision making on health policy. NICE set parameters and recommendations upon which NHS England, Wales and Northern Ireland will often base national, regional and local healthcare commissioning. However, the impact of NICE’s recommendations are far reaching because their reviews are publicly available and readily generalisable to other centrally funded healthcare systems thus a positive or negative decision by NICE can have market implications beyond the UK.

When considering novel or emerging treatments, NICE compares the new healthcare intervention (e.g., MRgFUS) to an existing treatment or standard of care (e.g., DBS) including cost and clinical effectiveness with particular regard to the outcomes of health technology assessments that demonstrate the Incremental Cost Effectiveness ratio (ICER) of the new intervention. To date, no cost-effectiveness study has been performed in the UK or Europe to assess MRgFUS in the treatment of ET.

Aims
This study assesses the cost-effectiveness of MRgFUS treatment for medically refractory Essential Tremor (mrET) in England; comparing MRgFUS treatment to both the current standard for those eligible for neurosurgical treatment (DBS with medication) and those ineligible for neurosurgical treatment (medication alone). The study considers the clinical effectiveness, safety profile, costing implications and the impact of quality of life for each treatment option in England.

METHODS AND MATERIALS
Model structure
A Markov cohort model was developed to estimate the cost-effectiveness of MRgFUS in England as a treatment for moderate to severe mrET in England. A Markov cohort model is commonly used for cost-effective analyses, following a cohort of patients through different health states over time; transitions between these health states are defined by a probability. This model was adapted from a model exploring the cost-effectiveness of MRgFUS in Canada; the structure and inputs were refined to ensure the approach was appropriate for an English population and the perspective of NHS England.

The model assessed MRgFUS in two subpopulations of mrET patients: mrET patients who are suitable for DBS and mrET patients who are not suitable for DBS (Figure 1). The two interventional strategies (DBS and MRgFUS) had the same model structure and used a cycle length of 1 year. The model approach
is described in Table 1 with further detail provided in Appendix 1.

The model included patients with moderate to severe mrET without previous intervention, i.e., patients undergoing DBS or MRgFUS for the first time. MrET was defined by a postural or intention tremor score of ≥2 on the Clinical Rating Scale for Tremor (CRST)26 and a minimum tremor-related disability cut off score of ≥2 on the disability subsection (Part C) of the CRST.27

Four health states were included in the model: baseline tremor (BT), mild to moderately improved tremor (MMT), marked improved tremor (MT), and tremor recurrence (TR).

- The BT state includes patients who live with disabling mrET if they do not undergo intervention or if they have an unsuccessful procedure (DBS or MRgFUS) defined as less than 10% improvement in their CRST score.
- The MMT and MT states include patients who have 10–50% improvement and 50–100% improvement in their CRST score respectively.24,25
- The TR is a transient one cycle state for patients who experience tremor recurrence after an intervention that requires re-operation.

Outcomes

Model outcomes were the total costs per patient (2019 GBP) and quality-adjusted life-years (QALYs) for each strategy over a 5-year time horizon based on the available temporal data for MRgFUS. QALYs are a measure of disease burden based on quantity and quality of life lived, commonly used in health outcomes analyses.30 The Incremental Cost-Effectiveness Ratio (ICER) is the cost per QALY gained when an intervention is introduced, which was calculated for MRgFUS versus DBS and for MRgFUS versus no procedure ((cost per MRgFUS – comparator) / (cost of MRgFUS – comparator)). A discount rate of 3.5% was applied to costs and utilities in the model in line with NICE guidelines.29

Model inputs

The model parameters are described in Table 2. The base case model included mrET patients starting at age 70 years in England. ET affects males and females equally,27 thus the proportion of males is based on Office for National Statistics (ONS) data.38 There are an estimated 26,202 patients with ET, of which 1,769 had moderate to severe mrET, and of those, 1,415 were eligible for DBS. Details are in Table S1; Appendix 241,38–41.

The proportion of the mrET population moving to each health state at each cycle was based on predicted population behaviour and response to treatment from the English Clinical Trial data42 (Table 1).

The costs were estimated from the perspective of NHS England and were reported in 2019 GBP. We included the following costs: surgical procedure, medication for ET, ongoing patient monitoring, and management of adverse effects (Table 1; details in Appendix 3 (Table S3-7; Appendix 3)). The DBS procedure cost was estimated using NHS reimbursement costs45 and validated by clinical experts (Appendix 3 Supplementary Table S3). The cost included all pre-, peri- and post-procedure and follow-up costs for the first year including all imaging and clinician time. For MRgFUS, the NHS England reimbursement cost was provided by Imperial College Healthcare NHS Trust included all pre-, peri-, post-procedure and follow-up costs for the first 5 years. The model assumes there are no costs associated with the transient or permanent adverse events for MRgFUS as they are managed during normal follow-up. All patients were assumed to have the same ET medications costs independent of which health state they were in. Costing details can be found in the Appendix 3 Supplementary Tables S3-7.

The approach to utility values is outlined in Table 1. Values included the utility in each health state, and the disutility incurred from treatment-related adverse events.

Uncertainty analyses

To explore the robustness of the base case results (derived from the baseline model inputs), uncertainty analyses were performed. A deterministic sensitivity analysis (DSA) and probabilistic sensitivity analyses (PSA) were performed to determine which parameters had the largest effect on model outcomes.

In the DSA, the input values for probabilities, utilities and costs were varied between their assigned upper and lower limits (either the 95% confidence interval (CI) from baseline or by 20% of the original values (Table S8; Appendix 3)). Only the results for those parameters that gave >5% difference from the base case, either using the high or low value, were reported.

A Monte Carlo PSA was run with 1,000 iterations. Each input value was independently sampled from their assigned distribution (based on data from the literature or estimated distributions). Probabilities were assigned a β distribution and cost parameters were assigned a γ distribution (Table S8; Appendix 3). All inputs shared by the two strategies (MRgFUS and DBS) were assigned the same value for that given iteration; all other input values were varied independently between the strategies. The probability of MRgFUS being cost-effective at different Willingness to Pay Thresholds (WTP) (i.e., different maximum values for an acceptable cost per gained QALY) was reported as a cost-effectiveness acceptability curve.

Five scenario analyses were run: 1) varying the starting age of patients in the model to age 40, 50 and 60; 2) varying the time-horizon; 3) modelling current care (i.e., a blend of patients who have no procedure and those that undergo the DBS procedure); 4) no discounting of costs and QALYs; and 5) using inputs from a North American Randomised Control Trial (RCT) to validate the English results.16 For scenario five sensitivity analyses (DSA, PSA) were performed again.

RESULTS

For the sub-population of mrET patients eligible for DBS, the model demonstrated the favourable cost-effectiveness of MRgFUS compared to DBS. MRgFUS was less costly (£19,779 vs £62,348) and more effective generating 0.03 additional QALYs.
Table 1. Outlining the model approach, probability inputs, costing inputs, utility and disutility values. Further costing detail is provided in the supplementary information (Table S3-7; Appendix 3).

| Model approach | Model Population | Inclusion criteria |
|----------------|------------------|--------------------|
|                |                  | Moderate to severe mrET defined as a postural or intention tremor score of ≥2 on the Clinical Rating Scale for Tremor (CRST).26 |
|                |                  | Minimum tremor-related disability cut off score of ≥2 on the disability subsection (Part C) of the CRST.27 |
|                |                  | Previous intervention for tremor e.g. DBS or MRgFUS. |
|                | Population Number| The number of patients in England with mrET was estimated using several assumptions (Table S1). |

| Time horizon   | 5 year time horizon |
|                | Incorporates expected differences between strategies e.g. Tremor recurrence, long-term adverse events |
|                | No long-term data for MRgFUS past 5 years28 |

| Discount rate  | 3.5% discount rate was applied to costs and utilities in the model in line with NICE guidelines.29 |

| Perspective    | Cost-utility analysis performed from the perspective of NHS England. |

| Construction   | Microsoft excel (Microsoft corporation, Redmond, Washington dc, USA). |

| Health states modelled | Four health states modelled |
|------------------------|----------------------------|
|                        | Baseline tremor (BT), Mild to Moderately improved tremor (MMT), Marked improved Tremor (MT), Tremor recurrence (TR). |

| Adverse events | Affect quality of life and/or incur healthcare costs. |
|----------------|------------------------------------------------------|
|                | Only included if they required physician input or had a large impact on quality of life (Table S2). |
|                | Transient defined <1year post procedure |
|                | Long term defined>1 year post procedure |

| Mortality | Assumptions included (literature referenced): |
|-----------|------------------------------------------------|
|           | No additional excess mortality from mrET nor procedures (DBS or MRgFUS).16 |
|           | At any point during the model time frame a patient may die from all-cause mortality |

| Probability Inputs | Improvement post-procedure |
|--------------------|----------------------------|
|                    | Assumptions included (literature referenced): |
|                    | MRgFUS and DBS have the same clinical effectiveness but with different adverse event profiles.30–32 |
|                    | Treatment benefit for MRgFUS is immediate.13 |
|                    | Treatment benefit for DBS starts at 3 months due to device optimisation (validated by clinical experts). |
|                    | MMT and MT proportions based on the English clinical trial18 with data augmentation using the Wilson Method (Appendix 1). |
|                    | Unsuccessful procedure considered less than 10% improvement, patients remained in BT health state. |

| Tremor Severity | Assumptions included (literature referenced): |
|-----------------|------------------------------------------------|
|                 | MrET stable over the time horizon, although ET is a naturally progressive disease. |
|                 | In the model patients only deteriorated due to tremor recurrence or waning procedural effectiveness. |

| Tremor recurrence | Assumptions included (literature referenced): |
|-------------------|------------------------------------------------|
|                   | For DBS, the probability of tremor recurrence (defined in the study as a pattern of tolerance) is 4%.20 |
|                   | For MRgFUS, the probability of recurrence is 8.3%.18 |
|                   | Recurrence rates were converted to an annual probability in the model assuming a constant probability over time. |

| Re-operation after tremor recurrence | Assumptions included (literature referenced): |
|--------------------------------------|------------------------------------------------|
|                                      | Re-operation resulted in the same outcomes as the primary procedure.25 |
|                                      | When TR patients undergo re-operation they receive the same surgical procedure as their first procedure. |

| Cost Inputs | Medication |
|-------------|------------|
|             | Assumptions included (literature referenced): |
|             | All patients have the same ET medications costs independent of which health state they were in. |
|             | Medication will continue to be taken despite a MT health state due to tremor in the untreated arm. |

| DBS | Estimated using NHS reimbursement costs33 and validated by clinical experts (Table S3). This cost included all pre-, peri- and post-procedure and follow-up costs for the first year. |

| MRgFUS | From the NHS England reimbursement costs provided by Imperial College Healthcare NHS Trust included all pre-, peri-, post-procedure and follow-up costs for the first 5 years. The model assumes there are no additional costs associated with the transient or permanent adverse events for MRgFUS as these are managed during routine follow-up. |

(Continued)
Cost-effectiveness of MRgFUS treatment for Essential Tremor in England

Table 1. (Continued)

| Utility values | Baseline Tremor (BT): | Based on Herceg et al., 2012 as per Canadian Model |
|----------------|-----------------------|--------------------------------------------------|
| Mild Tremor Improved (MT) | Based on Herceg et al., 2012 as per Canadian Model |
| Marked to Moderate Tremor Improvement (MMT): | The utility was assumed to be an average between BT and MT |
| Tremor Recurrence (TR): | The utility of TR was assumed to be the same as BT. |

Disutility values

| Reoperation | Assumptions included: |
|-------------|-----------------------|
| – No additional disutility associated with re-operation |
| – Any adverse events were captured in the same manner as for the first procedure. |
| Adverse Events | To include decreases in quality of life due to the transient and permanent adverse events, a weighted disutility was calculated using this four-step process outlined in appendix 1. |

(3.71 vs 3.68) per patient over the 5-year time horizon (Table 3). Thus MRgFUS is economically dominant compared to DBS.

In patients not suitable for DBS, the MRgFUS strategy cost over £16,000 more than medication alone (£19,779 vs £3,735) but yielded 0.77 additional QALYs (3.71 vs 2.95) per patient, producing an ICER of £20,851 per QALY gained over a 5-year horizon. This ICER falls within the NICE willingness to pay threshold of £20,000–30,000 per QALY and thus demonstrates the likely cost-effectiveness of unilateral MRgFUS for the treatment of mrET.

Deterministic sensitivity analysis (DSA)

The impact of varying the model inputs on the results is presented in a tornado graph (Figure 2) showing the difference between the MRgFUS and DBS strategies.

DSA results for MRgFUS versus DBS demonstrated that when the input parameters were varied between their low and high values, several parameters had the biggest impact on the ICER: the utility for the marked improvement health state in the first year for those undergoing MRgFUS (-£20,561,429 to -£697,086), the utility for baseline state in the first year for those undergoing DBS (-£672,348 to -£13,748,994), and the probability of recurrence for those undergoing DBS (-£4,720,374 to -£4,118,743).

DSA for MRgFUS versus no procedure demonstrated these inputs impacted the ICER most: the baseline utility (£12,517–62,397), the cost of MRgFUS procedure (£16,535–25,167) and utility for the marked improvement health state in year two onwards for those undergoing MRgFUS (£25,504–18,691).

Probabilistic sensitivity analysis (PSA)

The impact on the outcomes of varying the parameter inputs in the PSA is shown in Figure 3. The probability of MRgFUS being cost-effective at different WTPs is reported as a cost-effectiveness acceptability curve (Figure 4).

There was large uncertainty in the results for MRgFUS versus DBS. The average ICER was -£1,032,614 per QALY. The MRgFUS strategy was more cost-effective than DBS in 100% of the 1,000 iterations.

For MRgFUS versus no procedure, the ICER 95% CI varied between £15,194 to £202,391 (average £22,268). When using a WTP threshold of £30,000, the MRgFUS strategy was more cost-effective than no procedure in 66% of the 1,000 iterations and in under 2 of iterations were the differences in QALYs negative.

Scenario analysis

When the starting age of patients entering the population was reduced (Table 4), the ICER remained dominant compared to DBS but there was little change in the incremental QALY (Table 4). Compared to no procedure, the ICER slightly reduced from £20,851 from the base case (aged 70) to £19,816 (aged 40).

The results were sensitive to the model time horizon (Table S10; Appendix 3). When a 1-year and 10-year time horizon were used MRgFUS was still the dominant strategy compared to DBS in the base case. Compared to no procedure, the ICER in the base case was £84,539 and £13,940 at the 1- and 10-year time horizon, respectively. The current care scenario showed that MRgFUS was always a cost-effective option, but it became the dominant strategy if at least 30% of the population was eligible for DBS (Table 5).

Using the RCT inputs for the English model produced similar cost-effective outcomes as the original base case (Table 3). Further details on the RCT scenario results and sensitivity analyses are provided in Appendices 2, 3 (S10, S11, S12), 4 (F1-F3). A scenario was also run without discounting showing similar results (Appendix 3, S13).

DISCUSSION

This study demonstrates the favourable cost-effectiveness profile of unilateral MRgFUS for the treatment of mrET in England. For MRgFUS versus DBS, the MRgFUS strategy was economically dominant (less costly with 0.03 additional QALYs per patient) over a 5-year time horizon. Compared to no procedure (in patients not suitable for DBS) the MRgFUS strategy cost £16,000 more but yielded 0.77 additional QALYs per patient, producing an ICER of £20,851 per QALY gained, over a 5-year time horizon. The results
were sensitive to analyses on assumptions regarding the time horizon, cost of MRgFUS, and utilities used.

Table 2. Model parameters Further detail is provided in the supplementary information (Table S1-7; Appendix 3)

| Parameter                                           | Value   | Source |
|-----------------------------------------------------|---------|--------|
| Clinical effectiveness                               |         |        |
| Proportion with marked improvement post-procedure  | 88.9%   | 18     |
| Proportion with mild to moderate improvement post-procedure | 10.0%   | 18     |
| Proportion with no improvement post-procedure       | 1.1%    | 18     |
| Annual proportion moving from marked to mild due to waning in surgical effectiveness (MRgFUS) | 9.2%    | 18     |
| Annual proportion moving from marked to mild due to waning in surgical effectiveness (DBS) | 7.7%    | 36     |
| Annual probability of recurrence in (MRgFUS)         | 1%      | 18     |
| Annual probability of recurrence in (DBS)            | 3.9%    | 36     |
| Annual probability of re-operation after recurrence  | 5%      | Assumption (based on expert opinion) |
| Costs                                               |         |        |
| DBS procedure (all resource use for 1 year)          | £47,627 | Table S3 |
| MRgFUS procedure (all resource use for 5 years)      | £16,500 | Assumption (based on expert opinion) |
| Medication cost per year                             | £744    | Table S3 |
| Ongoing monitoring costs                             |         |        |
| No procedure                                        | £169    | Table S6 |
| DBS 2 + years                                       | £3,172  | Table S6 |
| MRgFUS 5 + years                                    | £169    | Table S6 |
| Adverse events costs                                |         |        |
| Infection                                           | £657    | Table S7 |
| Intracranial haemorrhage                            | £20,545 | Table S7 |
| Lead fracture or migration                          | £14,777 | Table S7 |
| Gait disturbance                                    | £0      | Table S7 |
| Speech problem                                      | £42     | Table S7 |
| Utilities                                           |         |        |
| Alive with disabling tremor (baseline)               | 0.69    | 34     |
| Improved tremor post-procedure (marked improvement – no adverse events) | 0.91    | 34     |
| Improved tremor post-procedure (mild to moderate improvement – no adverse events) | 0.80    |        |
| Improved tremor post-procedure with adverse events (marked improvement) (MRgFUS) | 0.91    | 0.90   |

(Continued)

Table 2. (Continued)

| Parameter                                           | Value   | Source |
|-----------------------------------------------------|---------|--------|
| Improved tremor post-procedure with adverse events (marked improvement) (DBS) Short term (year 1) | 0.91    | 0.91   |
| Improved tremor post-procedure with adverse events (mild/moderate improvement) (MRgFUS) Short term (year 1) | 0.80    | 0.79   |
| Improved tremor post-procedure with adverse events (mild/moderate improvement) (DBS) Short term (year 1) | 0.80    | 0.76   |
| Improved tremor post-procedure with adverse events (marked improvement) (MRgFUS) Short term (year 1) | 0.91    | 0.90   |

DBS, deep brain stimulation; MRgFUS, magnetic resonance-guided focused ultrasound.

were sensitive to analyses on assumptions regarding the time horizon, cost of MRgFUS, and utilities used.

Health policy

In the UK, NICE typically recommends interventions with ICERs at £20,000–£30,000; this is considered their WTP threshold. Although not a rigid formula, interventions with ICERs below or within the WTP threshold are more likely to be commissioned than those with higher ICERs. The ICER of £20,851 per QALY gained falls within NICE’s WTP supporting the view that MRgFUS should be adopted into standard practice in the treatment of mrET.

This study demonstrates to health policymakers that MRgFUS is an advantageous curative treatment option for mrET which can reduce tremor, improve quality of life and be cost-effective. MRgFUS benefits patients as it is a non-invasive procedure with a favourable safety profile that can be performed as a day case without general anaesthetic. Patients have immediate results without the need for ongoing optimisation or follow up. MRgFUS can also benefit the healthcare system, as MRgFUS falls within acceptable WTP levels it can save costs and/or inform rational allocation of resources. As the model (including
its assumptions and inputs) were from the perspective of NHS England, its outcomes may be helpful to other similarly publicly funded healthcare systems.

Limitations

The study limitations centered mainly on model inputs and assumptions. Inputs were selected by a combination of literature review, known costs, predicted and estimated costs, expert opinion and/or a combination of all. The robustness of these inputs were constrained by the quality of available data on mrET, MRgFUS and DBS. Where there was incomplete or no data, assumptions were needed. Where possible these assumptions were validated by clinical experts. For example, MRgFUS and DBS were assumed to be equally clinically effective although no head-to-head clinical trials have been performed. Of note, the scenario and sensitivity analyses tested the robustness of these assumptions and consistently determined MRgFUS to be cost-effective. Some key limitations and assumptions are described here.

As the model was designed for the NHS England perspective, English data inputs were utilised in the base case. However, as the English clinical trial was a small-scale study, the results were compared to using data inputs from a larger scale MRgFUS Randomised Control Trial53; this produced similar cost-effective outcomes as the original base case, and hence supported the robustness of results.

The model assumed that all patients suitable for DBS are equally suitable for MRgFUS. Although there may be some patients whose skull density ratio makes them ineligible for MRgFUS. This is a very low proportion of patients that is unlikely to make a difference to the model outcomes.

As there are few longitudinal studies for MRgFUS or DBS, any assessment on the long-term efficacy of treatment is challenging thus the model was not extrapolated over a patient's lifetime. The battery used in England has a longer life than the model time horizon,44 therefore costs did not include battery change for DBS however this would be a significant cost if included (Table S4, Appendix 3).

There are few studies reporting utility values for ET or mrET, thus utility values were taken from other neurological diseases. These assumptions are imperfect but provided insight into the disutility of chronic progressive disease.

Table 3. The baseline results for the outcomes (MRgFUS versus all comparators) per patient; 5-year horizon

| Strategy                     | Costs (£) | Δ Cost (£) | QALY | Δ QALY | ICER (£/QALY) |
|------------------------------|-----------|-----------|------|--------|---------------|
| Base case (England data)     | MRgFUS    | 19,779    | 3.71 |       |               |
| No procedure                 | 3,735     | 16,044    | 2.95 | 0.77   | 20,851        |
| DBS                          | 62,348    | −42,569   | 3.68 | 0.03   |               |
| Scenario based on RCT data   | MRgFUS    | 19,772    | 3.52 |       |               |
| No procedure                 | 3,735     | 16,037    | 2.95 | 0.57   | 27,959        |
| DBS                          | 61,531    | −41,759   | 3.44 | 0.08   |               |

The change in costs and QALYs is the comparator strategy always compared to the MRgFUS strategy i.e., the average change and ICER and not estimating the incremental gains. Difference and total costs values are reported to the nearest integer. Baseline results are with discounting. MRgFUS, magnetic resonance-guided focused ultrasound; DBS, deep brain stimulation; ICER, incremental cost-effectiveness ratio; QALY, Quality Adjusted Life Year

Δ = the difference in cost or QALY (MRgFUS – comparator strategy). A strategy is termed as dominant when it is both cost-saving (i.e., a negative incremental cost) and more effective (i.e., a positive incremental QALY).

Figure 2. Results of the deterministic sensitivity analysis for A) MRgFUS vs No Procedure B) MRgFUS vs DBS: the impact on the ICER of varying each parameter individually to the high and low values in a one-way sensitivity analysis.

Figure 3. Result of probabilistic analysis for MRgFUS vs No Procedure and MRgFUS vs DBS: based on 1,000 iterations illustrating the distribution of the ICERs.
Patient preference was assumed to be equal between MRgFUS and DBS. However, depending on their level of disability patients may have difficulty attending numerous follow-up appointments for DBS or may be unwilling to accept the risks associated with invasive surgery. MRgFUS may be preferable to patients ceteris paribus.

Comparison with other MRgFUS cost-effectiveness studies

Results from this study are comparable with other international MRgFUS cost-effectiveness studies. Similar to this study, a US study found MRgFUS to be less costly and more clinically effective than DBS. A Japanese study looked at costs alone and also found MRgFUS to be cheaper than DBS. However, these Japanese and American studies did not ascertain ICERs. The ICERs and outcomes for the Canadian study were similar to this study.

In the US study, the cost and the clinical effectiveness were calculated individually “measured by amount of utility added by the procedure”. The effectiveness value for MRgFUS was 0.194 vs 0.134 for DBS. DBS cost more (£22,450; converted 2016 US$27,906) than MRgFUS (£16,567; converted 2016 US $20,593). In the 2018 Canadian study, MRgFUS compared to no procedure had an ICER of £27,636 (converted from 2017 CAN$45,817) and MRgFUS was cheaper than DBS but less effective (ICER DBS versus MRgFUS of £78,927 (converted 2017 CAN$130,850)). The 2019 Japanese cost minimisation study (no quality of life estimate) was performed over 1 year. MRgFUS was determined cost-saving (£2,892; converted 2018 JPY400,380); the total costs per procedure for MRgFUS £15,494 (converted 2018 JPY2,145,037) and unilateral DBS were £18,386 (converted from 2018 JPY2,545,417).

Table 4. The results for the outcomes (MRgFUS versus all comparators, per patient); Age scenario (England data)

| Age | Costs (£) | Δ Cost (£) | QALY | Δ QALY | ICER (£/QALY) |
|-----|-----------|------------|------|--------|---------------|
| 60  | MRgFUS    | 19,892     |      | 3.84   |               |
|     | No procedure | 3,867 | 16,025 | 3.05 | 0.79 | 20,175 |
|     | DBS       | 62,914     | −43,023 | 3.81 | 0.03 | MRgFUS is dominant |
| 50  | MRgFUS    | 19,937     |      | 3.89   |               |
|     | No procedure | 3,920 | 16,017 | 3.09 | 0.80 | 19,917 |
|     | DBS       | 63,141     | −43,204 | 3.86 | 0.03 | MRgFUS is dominant |
| 40  | MRgFUS    | 19,955     |      | 3.91   |               |
|     | No procedure | 3,941 | 16,014 | 3.10 | 0.81 | 19,816 |
|     | DBS       | 63,231     | −43,276 | 3.88 | 0.03 | MRgFUS is dominant |

The change in costs and QALYs is the comparator strategy always compared to the MRgFUS strategy i.e., the average change and ICER and not estimating the incremental gains. Difference and total costs values are reported to the nearest integer. DBS, deep brain stimulation; MRgFUS, magnetic resonance-guided focused ultrasound; ICER, incremental cost-effectiveness ratio; QALY, Quality Adjusted Life Year

Δ = the difference in cost or QALY (MRgFUS – comparator strategy). A strategy is termed as dominant when it is both cost-saving (i.e., a negative incremental cost) and more effective (i.e., a positive incremental QALYs).
Cost-effectiveness of MRgFUS treatment for Essential Tremor in England

Table 5. The results for the outcomes per patient (assuming 100% of patients are suitable for MRgFUS versus a certain % of patients are not suitable for DBS): Current care scenario (England data)

| Strategy         | Patients eligible for DBS (%) | Costs (£) | Δ^1 Cost (£) | QALY | Δ^1 QALY | ICER (£/QALY) |
|------------------|-------------------------------|-----------|--------------|------|----------|---------------|
| MRgFUS           |                               | 19,779    | 16,044       | 2.95 | 0.77     | 20,851        |
| Current care     | 0                             | 5,735     |              |      |          |               |
|                  | 10                            | 9,716     |              |      |          |               |
|                  | 20                            | 15,670    |              |      |          |               |
|                  | 30                            | 21,597    |              |      |          |               |
|                  | 40                            | 27,498    |              |      |          |               |
|                  | 50                            | 33,373    |              |      |          |               |
|                  | 60                            | 39,221    |              |      |          |               |
|                  | 70                            | 45,042    |              |      |          |               |
|                  | 80                            | 50,837    |              |      |          |               |
|                  | 90                            | 56,606    |              |      |          |               |
|                  | 100                           | 62,348    |              |      |          |               |

Costs are per patient and QALYs are per patient; in both scenarios, DBS and MRgFUS, all patients had treatment at the 1-year mark. Delta costs and QALYs are the difference compared to the comparator strategy, and the incremental cost-effectiveness ratio is $\Delta\text{ICER} = \Delta\text{ICER} = \text{ICER} - \text{ICER}$. A strategy is termed as dominate when it is both cost-saving (i.e., a negative incremental cost) and more effective (i.e., a positive incremental QALY).

Future research

As the main challenge to estimating the cost-effectiveness was a lack of data, further research would benefit from improved data inputs. This could be attained through head-to-head RCT trials of MRgFUS and DBS, more longitudinal studies of MRgFUS and DBS considering long term efficacy, and ascertaining the utilities for mrET and patient treatment preferences. The DSA demonstrated particular sensitivity to utility values for both MRgFUS and DBS, dedicated studies ascertaining these inputs would improve any future cost-effectiveness analyses.

The model compared unilateral MRgFUS to unilateral DBS, ignoring the possibility of bilateral DBS treatments. Although there have been successful bilateral treatments for mrET using MRgFUS,[49–51] it is not yet standard of clinical practice in the UK and has not yet been commissioned by NHS England. Future research could compare bilateral MRgFUS to bilateral DBS.

CONCLUSION

This study demonstrates the favourable cost-effectiveness of MRgFUS for the treatment of mrET in England; in patients who are suitable and those who are not suitable for DBS, MRgFUS was deemed cost-effective. As the first European study, outcomes from this study can provide a basis for future commissioning of brain MRgFUS treatments in the UK, Europe and worldwide. MRgFUS can benefit patients and the healthcare systems and should be considered as a treatment option for mrET patients.

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