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Evidence review: Transcranial magnetic resonance-guided focused ultrasound thalamotomy for essential tremor

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Contents

1 Introduction

Introduction

- Essential tremor (ET) is the most common movement disorder (Louis and Ferreira 2010).
- ET causes uncontrolled oscillatory movements of the hands and arms which are usually bilateral. The head, jaw, face, legs and trunk may also be involved but less commonly than the hands. ET increases in severity over time so that in its later stages it may have a severe impact on the patients' quality of life, leading to social isolation and an inability to carry out ordinary activities of daily living such as dressing, using a phone, writing, drinking and eating. Stress commonly exacerbates ET, so that disability increases in stressful social situations (for example dining-out) often rendering the patient reclusive.

Existing guidance from the National Institute of Health and Care Excellence (NICE)

- In June 2018, NICE issued interventional procedures guidance about unilateral trans-cranial magnetic resonance-guided focused ultrasound (TcMRgFUS) thalamotomy for treatment-resistant essential tremor (NICE 2018). Thalamotomy is the destruction of tissue in the thalamus, part of the brain which relays motor and sensory signals to the cerebral cortex. NICE determined that "the evidence on the safety of unilateral MRI-guided focused ultrasound thalamotomy for treatment-resistant essential tremor raises no major safety concerns. However, current evidence on its efficacy is limited in quantity".
- NICE recommended that *'this procedure should not be used unless there are special arrangements for clinical governance, consent, and audit or research'.* The recommendations also state that:

  '1.2 Clinicians wishing to do unilateral MRI-guided focused ultrasound thalamotomy for treatment-resistant essential tremor should:

  - *Inform the clinical governance leads in their NHS trusts.*
  - *Ensure that patients and their carers understand that this procedure is only done to treat tremor on 1 side of the body, and that the effect of this on the functional ability and quality of life of patients with bilateral disease is uncertain. Patients should be informed about alternative treatments, including those that can be done bilaterally. Provide patients with clear written information to support shared decision-making. In addition, the use of NICE's information for the public is recommended.*
  - *Audit and review clinical outcomes of all patients having unilateral MRI-guided focused ultrasound thalamotomy for treatment-resistant essential tremor. NICE has identified relevant audit criteria and has developed an audit tool (which is for use at local discretion).*

  1.3 Patient selection should be done by a multidisciplinary team experienced in managing essential tremor, including clinicians with specific training in the procedure.

  1.4 Further research, which could include randomised controlled trials, should address patient selection, report on functional improvement and quality of life, and provide long-term follow-up data.'

The indication and epidemiology

- The overall prevalence of ET is about 0.9%. The prevalence increases markedly with age (≥65 years old = 4.6%, ≥95 years old = 21.7%). The age of onset of ET is bimodal with peaks at age 15 years of age and at 50 to 70 years of age (Brin and Koller 1998). Although some patients with ET also have Parkinson's disease, the two diseases are distinct.
- The causes of ET are not known, although in about 50% of cases it is considered to be familial. The pathological mechanisms underlying ET are known to involve complex circuitry within the brain that includes the cerebellum, inferior olive, zona incerta, thalamus and motor cortex.

Standard treatment and pathway of care

- Pharmacotherapy is the first line of treatment for ET and consists of first-line drugs such as propranolol and primidone, and second-line drugs such as topiramate, gabapentin and benzodiazepines.
- All these medications have poor benefit-to-adverse-effect ratios for patients with ET. Over time, many patients develop resistance to pharmacological treatments after which side-effects become more prominent than useful symptomatic benefit.
- They may then be treated with deep brain stimulation (DBS). This procedure involves inserting very fine needles into the brain through small holes made in the skull to determine the exact site of treatment. This part of the procedure is usually carried out under local anaesthetic. Once the treatment target is identified, a permanent electrode is placed into it. Under general anaesthetic, this electrode is then connected to a pulse generator implanted subcutaneously on the anterior chest wall.
- NHS England currently commissions DBS for patients with ET.
- NICE concluded in 2006 that “Current evidence on the safety and efficacy of deep brain stimulation for tremor and dystonia (excluding Parkinson's disease) appears adequate to support the use of this procedure, provided that the normal arrangements are in place for consent, audit and clinical governance” (NICE 2006).
- Stereotactic radiosurgery (SRS) is a highly conformal radiotherapy treatment to a precisely delineated target volume, delivered using stereotactic localisation techniques, delivered in a single fraction. SRS can be used to make a lesion in the area responsible for the uncontrolled movements. NHS England does not commission SRS for familial ET.
- Radiofrequency ablation (RFA) is a surgical procedure that directs a heat source to a specifically targeted tissue resulting in its destruction. RFA has also been used for the treatment of essential tremor in the past; some clinicians see it as superseded by DBS, while others still offer it to selected patients.

The intervention (and licensed indication)

- TcMRgFUS thalamotomy is carried out with the patient lying supine inside a magnetic resonance imaging (MRI) scanner. The patient's head is shaved and a stereotactic head frame is attached. Patients are kept awake so they can report any improvement or adverse events to the operator during the procedure. Continuous MRI and thermal mapping are used to identify the target area of the brain and monitor treatment. Low-power (sub-lethal) ultrasound is delivered to confirm the chosen location. Then, high-power focused ultrasound pulses are administered to irreversibly ablate target tissue. Chilled water is circulated around the head during the treatment to prevent thermal damage to the scalp caused by the increase in bone temperature. The procedure takes about three hours.

Rationale for use

- The potential benefits of TcMRgFUS thalamotomy for ET are that it is less invasive than other procedures, has a faster recovery time and allows for testing of the effects of sub-lethal doses before ablation. It may be safer and less expensive than alternative treatments.

2 Summary of results

- This rapid evidence review identified six studies which met the inclusion criteria. Four were comparisons of TcMRgFUS thalamotomy and DBS: two retrospective unrandomised controlled studies (Kim et al 2017 and Huss et al 2015) and two cost utility modelling studies (Li et al 2019 and Ravikumar et al 2017). Li et al (2019) also reported results of cost utility modelling for TcMRgFUS thalamotomy versus no treatment. There was also a randomised trial of TcMRgFUS thalamotomy versus sham treatment (Elias et al 2016) and an uncontrolled study reporting later results for this study, after nearly all participants had received TcMRgFUS thalamotomy (Chang et al 2018).

- The studies reported a number of outcomes including the effects of treatment on tremor and quality of life, and the cost-effectiveness and adverse effects of treatment. Studies selected for inclusion in this review did not report results for any subgroups that may benefit from TcMRgFUS more than the wider population of interest.

Clinical Effectiveness

TcMRgFUS thalamotomy for essential tremor compared with DBS

- **Successful treatment at one month (one study, n=59):** Kim et al (2017) reported rates of successful treatment[1] at one month after TcMRgFUS thalamotomy of 21/23 (91%) and after DBS of 17/19 (89%). No p-values were reported.
- **Complete remission at one month (one study, n=59):** Kim et al (2017) reported rates of complete remission at one month after TcMRgFUS thalamotomy of 10/23 (43%) and after DBS of 6/19 (32%). No p-values were reported.
- **Successful treatment at twelve months (one study, n=59):** Kim et al (2017) reported rates of successful treatment at twelve months after TcMRgFUS thalamotomy of 18/23 (78%) and after DBS of 16/19 (84%). No p-values were reported.
- **Complete remission at twelve months (one study, n=59):** Kim et al (2017) reported rates of complete remission at twelve months after TcMRgFUS thalamotomy of 8/23 (35%) and after DBS of 9/19 (47%). No p-values were reported.
- **Change in Clinical Rating Scale for Tremor (CRST) total score[2]: (one study, n=85)** Huss et al (2015) reported post-procedure CRST scores as follows: bilateral DBS 13.2 (79.5% improvement from baseline), unilateral DBS 15.8 (62.8% improvement from baseline) and TcMRgFUS thalamotomy 17.7 (55.7% improvement from baseline). All three procedures were reported as improved versus baseline ($p<0.05$), and the second two procedures were reported as different from bilateral DBS ($p<0.05$). Pre-treatment scores were not reported, nor were there reported comparisons of unilateral DBS with TcMRgFUS thalamotomy.

[1] Defined as absent tremor (complete remission) or occasional tremor (greater than 90% improvement) on the Fahn-Tolosa-Marin scale. This scale contains sections for assessing rest, postural and kinetic/intention tremor amplitude in specific anatomic locations (Part A), tremor in writing, drawing, and pouring (Part B), activities of daily living (Part C) and global assessments by the patient and examiner (Part D), with each item rated on a scale from 0 to 4. Higher scores indicate worse tremor.

[2] The CRST is used to assess the severity of tremor. It has three parts: Part A (observed tremor), Part B (tasks) and Part C (disability), each scored from 0 to 4; higher scores indicate more severe tremor. Part A separately scores resting, postural, and action or intention components of hand tremor. Higher scores indicate worse tremor.

- **Proportion of participants with CRST tremor score of 2 to 4 in dominant hand pre-procedure who had a score of 0 to 1 post-procedure (one study, n=85):** Huss et al (2015) reported the following results for this outcome: bilateral DBS 46/55 (83.6%), unilateral DBS 11/13 (84.6%), TcMRgFUS thalamotomy 12/15 (80%) (p>0.05 for comparison between treatments).
- **Proportion of participants with CRST handwriting score of 3 to 4 pre-procedure who had a score of 0 to 2 post-procedure (one study, n=85):** Huss et al (2015) reported the following results for this outcome: bilateral DBS 20/26 (76.9%), unilateral DBS 7/8 (87.5%), TcMRgFUS thalamotomy 6/7 (86.7%) (p>0.05 for comparison between treatments).
- **QUEST summary score[3] (one study, n=85:)** Huss et al (2015) reported mean pre- and post-procedure scores as follows: bilateral DBS 52.1, 72.0; unilateral DBS not reported; TcMRgFUS thalamotomy 37.5, 68.0. Although scores for both procedures rose, indicating poorer quality of life, both post-procedure scores were reported as showing "significant improvements" versus baseline (p<0.05), but not showing different improvement between procedures. SPH contacted the authors about this apparent error but received no reply.

TcMRgFUS thalamotomy for essential tremor compared with sham treatment

- **Change in mean CRST hand tremor score[4] at three months (one study, n=76):** Elias et al (2016) reported the following mean CRST hand tremor scores for TcMRgFUS thalamotomy: pre-treatment 18.1, three months post-treatment 9.6. For sham treatment, the results were pre-treatment 16.0 and three months post-treatment 15.8. The difference was 8.3 points (95% confidence interval (CI) 5.9 to 10.7, p<0.001).
- **Change in mean CRST hand tremor score at 12 months (one study, n=76):** Elias et al (2016) reported the following mean CRST hand tremor scores for TcMRgFUS thalamotomy: pre-treatment 18.1 and three months post-treatment 10.9. Results for sham treatment were not reported. The difference between the two treatments was reported as 7.2 points (95% CI 6.1 to 8.3, p<0.001).
- **Change in mean CRST disability score at three months (one study, n=76):** Elias et al (2016) reported the following mean CRST disability scores for TcMRgFUS thalamotomy: pre-treatment 16.5 and three months post-treatment 6.2. For sham treatment, the results were pre-treatment 16.0 and three months post-treatment 15.6. The difference was 9.9 points (p<0.001).
- **Change in mean QUEST score at three months (one study, n=76):** Elias et al (2016) reported the following mean QUEST scores for TcMRgFUS thalamotomy: pre-treatment 42.6 and three months post-treatment 23.1. For sham treatment, the results were pre-treatment 42.8 and three months post-treatment 41.1. The difference between the two treatments was 17.8 points (p<0.001).

  No other results were reported.

TcMRgFUS thalamotomy for essential tremor (no comparator)

- **Change in mean CRST hand tremor score at 24 months (one study, n=67):** Chang et al (2018) reported the following mean CRST hand tremor scores for TcMRgFUS thalamotomy: pre-treatment 19.8 and 24 months after treatment 8.8. The difference was 11 points (95% CI 7.6 to 10.0, p<0.001).

[3] The Quality of Life in Essential Tremor Questionnaire (QUEST) includes 30 items in five domains (physical, psychosocial, communication, leisure and work/finance). Higher scores indicate lower quality of life.

[4] This hand tremor score (on a scale ranging from 0 to 32, with higher scores indicating more severe tremor) was derived from the CRST, Part A (three items: resting, postural, and action or intention components of hand tremor), and the CRST, Part B (five tasks involving handwriting, drawing, and pouring), in the hand contralateral to the thalamotomy.

- **Change in mean CRST disability score at 24 months (one study, n=67):** Chang et al (2018) reported the following mean CRST disability scores for TcMRgFUS thalamotomy: pre-treatment 16.4 and 24 months after treatment 6.5. The difference was 9.9 points (95% CI 5.3 to 7.7, p<0.001).

Safety

The safety outcome reported was adverse effects of treatment. No study reported tests of the significance of any differences in rates of adverse effects.

TcMRgFUS thalamotomy for essential tremor compared with DBS

- **Adverse effects (two studies, n=59 and n=85):** Kim et al (2017) reported the following adverse effects of TcMRgFUS thalamotomy: mild facial paresis for first month after procedure 1/23 (4%); balance problems due to brain oedema for first month after procedure, controlled with oral steroid therapy plus mild facial paresis still present at 12 month 1/23 (4%). For DBS, the reported adverse effects were mild facial paresis for first month after procedure 1/19 (5%); balance problems relieved with stimulation adjustment 3/19 (16%); and muscle twitching in the contralateral forearm 1/19 (5%). Huss et al (2015) reported a paraesthesia rate of 3/15 (20%) after TcMRgFUS thalamotomy. For bilateral DBS, the reported adverse effects were paraesthesia 1/57 (1.8%), dysarthria 6/57 (11%), weakness 1/57 (1.8%), mental state change 3/57 (5.3%), hardware infection 1/57 (1.8%) and lead erosion 2/57 (3.5%). For unilateral DBS, the reported adverse effects were paraesthesia in 2/13 (15%).

TcMRgFUS thalamotomy for essential tremor compared with sham treatment

- **Adverse effects (one study, n=76):** Elias et al (2016) reported the following adverse effects after TcMRgFUS thalamotomy: gait disturbance in 36% and paraesthesias or numbness in 38%, persisting for 12 months in 9% and 14% of patients respectively. One patient had dense and permanent hypaesthesia of the dominant thumb and index finger, categorised as a serious adverse event. One patient had a transient ischaemic attack six weeks after undergoing thalamotomy. Among the patients treated with sham treatment, one (5%) reported paraesthesia, one (5%) reported subjective unsteadiness or imbalance, four (20%) reported headache for more than a day and one (5%) reported fatigue.

TcMRgFUS thalamotomy for essential tremor (no comparator)

- **Adverse effects (one study, n=67):** Chang et al (2018) reported that none of the adverse events reported in Elias et al (2016) worsened at two years follow-up and that two of these events resolved (dysergia and paraesthesia). There were no new adverse events in the participants reported during the second year of follow-up.

Cost Effectiveness

The cost effectiveness outcome reported was the incremental cost effectiveness ratio.

TcMRgFUS thalamotomy for essential tremor compared with DBS

- **Incremental cost effectiveness ratio (two modelling studies):** Li et al (2019) reported an estimated incremental cost of DBS vs TcMRgFUS thalamotomy of Canadian$34,026

(£20,200)[5], an estimated incremental utility of 0.26 QALYs over five years and an estimated incremental cost effectiveness ratio (ICER) of C$130,850 (£77,700) per QALY. Ravikumar et al (2017) reported that TcMRgFUS thalamotomy cost an estimated US$20,593 (£16,140)[6] and yielded an estimated 0.194 QALYs. DBS without staging cost an estimated US$27,906 (£21,900) and yielded an estimated 0.134 QALYs.

TcMRgFUS thalamotomy for essential tremor compared with no treatment

- **Incremental cost effectiveness ratio (one modelling study):** Li et al (2019) reported an estimated incremental cost of TcMRgFUS thalamotomy vs no surgery of C$21,438 (£12,700), an estimated incremental utility of 0.47 QALYs over five years and an estimated incremental cost utility $45,817 (£27,200) per QALY.

Subgroups that may benefit from TcMRgFUS more

Studies selected for inclusion in this review did not report results for any subgroups that may benefit from TcMRgFUS more than the wider population of interest.

Definitions of essential tremor, treatment-refractory tremor and severity scores of essential tremor

Elias et al (2016) defined essential tremor as "characterized by a distinctive postural and intention tremor typically affecting the hands more than the legs, trunk, head, or voice." The other included studies which included a definition were consistent with this.

Elias et al (2016) defined treatment-refractory tremor as "tremor that was refractory to at least two trials of medical therapy, including at least one first-line agent (propranolol or primidone)." The other five studies included in this review did not report a definition of the term.

Conclusions

Elias et al (2016) is a reliable randomised trial indicating that TcMRgFUS thalamotomy is more effective than sham treatment, but is associated with a risk of gait disturbance, paraesthesia and numbness. Chang et al (2018) indicates effects of treatment reported by Elias et al (2015) are still present two years later, and suggests that some adverse effects may improve while others do not emerge within this period of follow-up. However, discrepancies in Chang et al (2018)'s reporting cast doubt on the accuracy of the data reported in this study.

TcMRgFUS thalamotomy may have advantages over DBS because it is less invasive. However, these are not reported in the two low quality studies (Kim et al 2017 and Huss et al 2015) comparing DBS with TcMRgFUS thalamotomy; these indicate that the treatment outcomes are similar. Both studies are of low quality, with a number of serious methodological weaknesses, and neither is reliable. Similarly, both the cost effectiveness studies are unsuitable for decision-making: Li et al (2019)'s conclusions rest on insecure assumptions and use Canadian healthcare costs, making them of little relevance to the NHS, while Ravikumar et al (2017) is affected by serious methodological weaknesses and is unreliable.

This evidence is consistent with NICE's recommendation that TcMRgFUS thalamotomy "should not be used unless there are special arrangements for clinical governance, consent, and audit or research."

[5] Currency conversion carried out by SPH
[6] Currency conversion carried out by SPH

3 Methodology

- The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).
- A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group for the topic (see section 9 for PICO).
- The PICO was used to search for relevant publications in the following sources: Pubmed, Embase, Cochrane library (see section 10 for search strategy).
- The search dates for publications were from 1st January 2009 to 15th May 2019.
- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion. Papers which matched the PICO were selected for inclusion in this review.
- Evidence from all papers included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using National Service Framework for Long term Conditions (NSF-LTC) evidence assessment framework (see section 7 below).
- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8 below).

4 Results

This rapid evidence review identified six studies which met the inclusion criteria. Four were comparisons of TcMRgFUS thalamotomy and DBS: two retrospective unrandomised controlled studies (Kim et al 2017 (n=59)) and Huss et al 2015 (n=85)) and two cost utility modelling studies (Li et al 2019 and Ravikumar et al 2017). Li et al also reported results of cost utility modelling for TcMRgFUS thalamotomy versus no treatment. There was also a randomised trial of TcMRgFUS thalamotomy versus sham treatment (Elias et al 2016 (n=76)) and an uncontrolled study presenting later results for this study, after nearly all participants had received TcMRgFUS thalamotomy (Chang et al 2018 (n=67)).

Full details of the study designs and outcomes are summarised in the evidence tables in section 7.

1) In patients with treatment refractory essential tremor, what is the clinical effectiveness of TcMRgFUS thalamotomy compared to DBS or conservative management (i.e. no treatment beyond drug therapy; this includes "sham" procedures conducted in the research literature)?

Clinical effectiveness outcomes reported were successful treatment[7] at one month, complete remission at one month, successful treatment at twelve months, complete remission at twelve months, change in Clinical Rating Scale for Tremor (CRST) total score[8], QUEST summary

[7] Defined as absent tremor (complete remission) or occasional tremor (greater than 90% improvement) on the Fahn-Tolosa-Marin scale. This scale contains sections for assessing rest, postural and kinetic/ intention tremor amplitude in specific anatomic locations (Part A); tremor in writing, drawing, and pouring (Part B); activities of daily living (Part C); and global assessments by the patient and examiner (part D), with each item rated on a scale from 0 to 4. Higher scores indicate worse tremor.

[8] The CRST is used to assess the severity of tremor. It has three parts: Part A (observed tremor), Part B (tasks) and Part C (disability), each scored from 0 to 4; higher scores indicate more severe tremor. Part A scores separately resting, postural, and action or intention components of hand tremor. Higher scores indicate worse tremor.

score[9], the proportion of participants with CRST tremor score of 2 to 4 in dominant hand pre-procedure who had a tremor score of 0 to 1 post-procedure, the proportion of participants with CRST handwriting score of 3 to 4 pre-procedure who had a tremor score of 0 to 2 post-procedure, change in mean CRST hand tremor score[10] at three months, change in mean CRST hand tremor score at twelve months, change in mean CRST disability score at three months, change in mean QUEST score at three months, change in mean CRST hand tremor score at 24 months and change in mean CRST disability score at 24 months.

TcMRgFUS thalamotomy for essential tremor compared with DBS

Successful treatment at one month

Kim et al (2017) reported rates of successful treatment[11] at one month after TcMRgFUS thalamotomy of 21/23 (91%) and after DBS of 17/19 (89%) (p-value not reported).

Complete remission at one month

Kim et al (2017) reported rates of complete remission at one month after TcMRgFUS thalamotomy of 10/23 (43%) and after DBS of 6/19 (32%) (p-value not reported).

Successful treatment at twelve months

Kim et al (2017) reported rates of successful treatment at twelve months after TcMRgFUS thalamotomy of 18/23 (78%) and after DBS of 16/19 (84%) (p-value not reported).

Complete remission at twelve months

Kim et al (2017) reported rates of complete remission at twelve months after TcMRgFUS thalamotomy of 8/23 (35%) and after DBS of 9/19 (47%) (p-value not reported).

Change in CRST total score

Huss et al (2015) reported post-procedure CRST scores as follows: bilateral DBS 13.2 (79.5% improvement from baseline), unilateral DBS 15.8 (62.8% improvement from baseline) and TcMRgFUS thalamotomy 17.7 (55.7% improvement from baseline). All three procedures were reported as improved versus baseline ($p<0.05$), and the second two procedures were reported as different from bilateral DBS ($p<0.05$). Pre-treatment scores were not reported, nor were there reported comparisons of unilateral DBS with TcMRgFUS thalamotomy.

Proportion of participants with CRST tremor score of 2 to 4 in dominant hand pre-procedure who had a score of 0 to 1 post-procedure

Huss et al (2015) reported no statistically significant between-group differences in reported improvements for this outcome: bilateral DBS 46/55 (83.6%), unilateral DBS 11/13 (84.6%), TcMRgFUS thalamotomy 12/15 (80%) ($p>0.05$ for comparison between treatments).

Proportion of participants with CRST handwriting score of 3 to 4 pre-procedure who had a score of 0 to 2 post-procedure

[9] The Quality of Life in Essential Tremor Questionnaire (QUEST) includes 30 items in five domains (physical, psychosocial, communication, leisure and work/finance). Higher scores indicate lower quality of life.

[10] This hand tremor score (on a scale ranging from 0 to 32, with higher scores indicating more severe tremor) was derived from the CRST, Part A (three items: resting, postural, and action or intention components of hand tremor), and the CRST, Part B (five tasks involving handwriting, drawing, and pouring), in the hand contralateral to the thalamotomy.

[11] Defined as absent tremor (complete remission) or occasional tremor (greater than 90% improvement) on the Fahn-Tolosa-Marin scale. This scale contains sections for assessing rest, postural and kinetic/ intention tremor amplitude in specific anatomic locations (part A); tremor in writing, drawing, and pouring (part B); activities of daily living (part C); and global assessments by the patient and examiner, with each item rated on a scale from 0 to 4. Higher scores indicate worse tremor.

Huss et al (2015) reported no statistically significant between-group differences in reported improvements for this outcome: bilateral DBS 20/26 (76.9%), unilateral DBS 7/8 (87.5%), TcMRgFUS thalamotomy 6/7 (86.7%) (p>0.05 for comparison between treatments).

QUEST summary score
Huss et al (2015) reported mean pre- and post-procedure scores as follows: bilateral DBS 52.1, 72.0; unilateral DBS not reported; TcMRgFUS thalamotomy 37.5, 68.0. Although scores for both procedures rose, indicating poorer quality of life, both post-procedure scores were reported as showing "significant improvements" versus baseline (p<0.05), but not showing different improvement between procedures. SPH contacted the authors about this apparent error but received no reply.

TcMRgFUS thalamotomy for essential tremor compared with sham treatment

Change in mean CRST hand tremor score at three months
Elias et al (2016) reported the following mean CRST hand tremor scores for TcMRgFUS thalamotomy: pre-treatment 18.1 and three months post-treatment 9.6. For sham treatment, the results were pre-treatment 16.0 and three months post-treatment 15.8. The between-group difference in improvement was 8.3 points (95% confidence interval (CI) 5.9 to 10.7, p<0.001).

Change in mean CRST hand tremor score at 12 months
Elias et al (2016) reported the following mean CRST hand tremor scores for TcMRgFUS thalamotomy: pre-treatment 18.1 and twelve months post-treatment 10.9. Results for sham treatment were not reported. The between-group difference in improvement was reported as 7.2 points (95% CI 6.1 to 8.3, p<0.001).

Change in mean CRST disability score at three months
Elias et al (2016) reported the following mean CRST disability scores for TcMRgFUS thalamotomy: pre-treatment 16.5 and three months post-treatment 6.2. For sham treatment, the results were pre-treatment 16.0 and three months post-treatment 15.6. The between-group difference in improvement was 9.9 points (p<0.001).

Change in mean QUEST score at three months
Elias et al (2016) reported the following mean QUEST scores for TcMRgFUS thalamotomy: pre-treatment 42.6 and three months post-treatment 23.1. For sham treatment, the results were pre-treatment 42.8 and three months post-treatment 41.1. The between-group difference in improvement was 17.8 points (p<0.001).

No other results were reported.

TcMRgFUS thalamotomy for essential tremor (no comparator)

Change in mean CRST hand tremor score at 24 months
Chang et al (2018) reported an improvement in the mean CRST hand tremor scores after TcMRgFUS thalamotomy: pre-treatment 19.8 and 24 months after treatment 8.8. The between-group difference in improvement was 11 points (95% CI 7.6 to 10.0, p<0.001)[12].

Change in mean CRST disability score at 24 months

[12] The authors' reported 95% CIs for changes in CRST scores do not include the reported value for this parameter. These discrepancies cast doubt on the accuracy of the data reported in this study.

Chang et al (2018) reported an improvement in the mean CRST disability scores for TcMRgFUS thalamotomy: pre-treatment 16.4 and 24 months after treatment 6.5. The between-group difference in improvement was 9.9 points (95% CI 5.3 to 7.7, p<0.001)[13].

2) **In patients with treatment refractory essential tremor, what is the safety of TcMRgFUS compared to DBS or conservative management?**

The safety outcomes reported were adverse effects of treatment. No study reported tests of the significance of any differences in rates of adverse effects.

TcMRgFUS thalamotomy for essential tremor compared with DBS

Kim et al (2017) reported the following adverse effects of TcMRgFUS thalamotomy: mild facial paresis for first month after procedure 1/23 (4%) and balance problems due to brain oedema for first month after procedure, controlled with oral steroid therapy plus mild facial paresis still present at 12 month 1/23 (4%). For DBS, the reported adverse effects were mild facial paresis for first month after procedure 1/19 (5%), balance problems relieved with stimulation adjustment 3/19 (16%), and muscle twitching in the contralateral forearm 1/19 (5%).

Huss et al (2015) reported a paraesthesia rate of 3/15 (20%) after TcMRgFUS thalamotomy. For bilateral DBS, the reported adverse effects were paraesthesia 1/57 (1.8%), dysarthria 6/57 (11%), weakness 1/57 (1.8%), mental state change 3/57 (5.3%), hardware infection 1/57 (1.8%) and lead erosion 2/57 (3.5%). For unilateral DBS, the reported adverse effects were paraesthesia in 2/13 (15%).

TcMRgFUS thalamotomy for essential tremor compared with sham treatment

Elias et al (2016) reported the following adverse effects after TcMRgFUS thalamotomy: gait disturbance in 36% and paraesthesias or numbness in 38%, persisting for 12 months in 9% and 14% of patients respectively. One patient had dense and permanent hypaesthesia of the dominant thumb and index finger, categorised as a serious adverse event. One patient had a transient ischaemic attack six weeks after undergoing thalamotomy. Among the patients treated with sham treatment, one (5%) reported paraesthesia, one (5%) reported subjective unsteadiness or imbalance, four (20% reported headache for more than a day and one (5%) reported fatigue.

TcMRgFUS thalamotomy for essential tremor (no comparator)

Chang et al (2018) reported that none of the adverse events reported in Elias et al (2016) worsened at two years follow-up and that two of these events resolved (dysergia and paraesthesia). There were no new adverse events in the participants reported during the second year of follow-up.

3) In patients with treatment refractory essential tremor, what is the cost-effectiveness of TcMRgFUS compared to DBS or conservative management?

TcMRgFUS thalamotomy for essential tremor compared with DBS

[13] The authors' reported 95% CIs for changes in CRST scores do not include the reported value for this parameter. These discrepancies cast doubt on the accuracy of the data reported in this study.

Li et al (2019) reported an estimated incremental cost of DBS vs TcMRgFUS thalamotomy of Canadian$34,026 (£20,200)[14], an estimated incremental utility of 0.26 QALYs over five years and an estimated ICER of C$130,850 (£77,700) per QALY.

Ravikumar et al (2017) reported that TcMRgFUS thalamotomy cost an estimated US$20,593 (£16,140)[15] and yielded an estimated 0.194 QALYs, reported as “effectiveness”. DBS without staging cost an estimated US$27,906 (£21,900) and yielded an estimated 0.134 QALYs, also reported as “effectiveness”. This implies that TcMRgFUS thalamotomy is dominant, being both more effective and less expensive.

TcMRgFUS thalamotomy for essential tremor compared with no treatment

Li et al (2019) reported an estimated incremental cost of TcMRgFUS thalamotomy vs no surgery of C$21,438 (£12,700), an estimated incremental utility of 0.47 QALYs over five years and an estimated ICER of C$45,817 (£27,200) per QALY.

4) From the evidence selected, are there any subgroups that may benefit from TcMRgFUS more than the wider population of interest (such as tremor severity)?

No evidence was identified relevant to this question.

5) From the evidence selected, what are the definitions of essential tremor, treatment-refractory tremor, and severity scores of essential tremor that are used?

Elias et al (2016) defined essential tremor as “characterized by a distinctive postural and intention tremor typically affecting the hands more than the legs, trunk, head, or voice.” Other studies which included a definition were consistent with this.

Elias et al (2016) defined treatment-refractory tremor as “tremor that was refractory to at least two trials of medical therapy, including at least one first-line agent (propranolol or primidone).” The other five studies did not report a definition of the term.

The studies reported severity of tremor using the CRST and the Fahn-Tolosa-Marin scale, and quality of life using QUEST.

5 Discussion

TcMRgFUS thalamotomy for essential tremor compared with DBS

Kim et al (2017) reports no important differences in clinical effectiveness or safety between TcMRgFUS thalamotomy and DBS. The study is of low quality and has a number of serious methodological weaknesses. Treatment allocation was not apparently concealed, so both participants and assessors may have been aware of which treatment was used, introducing potential bias. The method by which treatments were allocated was not reported, so patients with different prognoses may have been preferentially allocated to one or other treatment. The study was retrospective, and the authors do not report whether all eligible patients were included, introducing the possibility of further bias. Also, the authors do not report how many people were

[14] Currency conversion carried out by SPH
[15] Currency conversion carried out by SPH

treated but not included because they were lost to follow-up; such patients may have had worse outcomes, introducing a further bias. The study was small, so may have lacked power to detect differences. Little can be concluded from this study.

Huss et al (2015) suggests that TcMRgFUS thalamotomy, unilateral and bilateral DBS are all effective. Apart from bilateral DBS being more effective than either of the other procedures for improving CRST total score, there were no reported differences between the procedures.

Huss et al (2015) has numerous serious methodological weaknesses:

Treatment allocation was not apparently concealed, so both participants and assessors may have been aware of which treatment was used, introducing potential bias.

The study was retrospective, and the authors do not report whether all eligible patients were included, introducing the possibility of further bias.

Allocation to unilateral or bilateral DBS treatment depended on whether the participant had unilateral or bilateral tremor, though three participants with bilateral symptoms “chose not to have the second side treated after unilateral [DBS] placement”, three “were recommended for unilateral treatment because of concerns regarding potential complications because of age and less cognitive reserve” and three others “had physical considerations (brain, skull, or scalp) that precluded bilateral treatment”. The comparison of unilateral and bilateral DBS is therefore potentially biased by the inclusion in the unilateral DBS group of patients with more extensive disease. This is corroborated by CRST scores indicating more severe disease in participants allocated to DBS.

The authors carried out 18 tests of statistical significance on their reported results of treatment, did not adjust the p-value and regarded as statistically significant those where $p<0.05$. Since they do not report p-values, we cannot tell which if any of these differences was significant[16].

Twelve patients, all treated with DBS, had “missing information or incomplete evaluations” and were excluded from the analysis. These patients may have had worse outcomes, introducing further bias. Since one participant with only three months of follow-up was included, it is unclear what the exclusion criteria were.

Participants undergoing unilateral DBS had shorter follow-up, though the authors report no test of the significance of this difference. For patients who underwent DBS, postoperative evaluation took place 3 to 24 months (mean follow-up, 13 months) after the patient’s device was turned on. For patients who underwent TcMRgFUS thalamotomy, CRST was evaluated at 12 months after surgery, except for one patient who only had a 3-month follow-up. These differences in follow-up are further source of bias.

Although higher QUEST scores indicate worse quality of life (confirmed by the authors (“QUEST summary index, (100% is worst)”), participants are reported as having higher QUEST scores after the procedures than before. Yet the authors report “After surgery, patients in both groups reported significant improvements in overall quality of life”. This contradiction casts further doubt on the reliability of the paper. We have raised this issue with the authors, but have yet to receive a reply.

[16] Bonferroni-adjusted p-value is 0.05/18=0.00278

For unilateral DBS procedures, “too few patients had preoperative and postoperative QUEST scores, so these patients were excluded from analysis of QUEST outcomes”. Bilateral DBS results are of limited relevance to this RER, as TcMRgFUS thalamotomy was only used for patients with unilateral tremor.

For these reasons, it is difficult to draw confident conclusions from this study by Huss et al (2015).

Li et al (2019)’s cost utility modelling indicated that DBS was not cost effective relative to TcMRgFUS thalamotomy, with an incremental cost effectiveness ratio (ICER) of £77,700 per QALY. This was based on the authors’ assumption that TcMRgFUS thalamotomy and DBS are equally effective in tremor abatement but have different adverse event profiles; there is no clear evidence in this rapid evidence review that the adverse event profiles differ. The authors’ utility estimates were derived from Herceg et al (2012), a study of drug treatment of essential tremor. Since this study was uncontrolled, the placebo effect may have exaggerated apparent treatment effects and therefore the utility gain from treatment. The authors do not report how capital costs of TcMRgFUS thalamotomy equipment was handled in this modelling; if it was excluded from the model, then adding it would decrease the incremental cost of DBS and improve its ICER. The analysis was based on Canadian healthcare costs, which differ from those in the NHS. This reduces the relevance of this analysis to the NHS.

Finally, Ravikumar et al (2017) report that TcMRgFUS thalamotomy is dominant to DBS, being both more effective and less expensive. This result is extremely unreliable.

The authors note that “Nearly all included reports represented uncontrolled observational studies and must be considered level 4 evidence”. Nevertheless, the authors did not carry out individual critical appraisal of the reports of clinical effectiveness and safety on which they relied for estimates of clinical effectiveness, taking no account of the risk that the results were undermined by bias. They did not use any quality threshold for inclusion and report no sensitivity analysis to explore the effect of excluding lower quality papers. They do not report calculating the reports’ heterogeneity before meta-analysing them.

The authors use improvement in the disability section of the CRST as their measure of treatment effect. They claim that “It has been shown that this improvement can be mapped on a parametric measure of quality of life known as the utility score based on patient preference for a given health state”. However, the reference that they cite in support of this (Martínez-Martín et al 2010) was a study to validate QUEST and did not report an association between CRST and quality of life. This casts serious doubt on the extent to which a change in CRST score, even if accurately measured, could be used as a reliable estimate of the impact of treatment on quality of life.

The authors intended to use US Medicare reimbursement costs for their model. However, “as Medicare reimbursement rates have not yet been determined for MRgFUS, these were estimated”. The authors do not report how they were estimated. Since NHS costs differ substantially from those in the United States, and the US costs were not of demonstrable accuracy, there is substantial risk in using analysis based on these costs for NHS decision-making.

The authors do not report what time horizon they used nor how they estimated the duration of life after treatment. They appear not to have discounted costs or benefits of treatment. Their reporting appears to confuse changes in CRST scores with quality-adjusted life years gained.

Because of these serious methodological defects, little confidence can be placed in this study's results.

TcMRgFUS thalamotomy for essential tremor compared with sham treatment

Elias et al (2016) is a reliable randomised trial, indicating that TcMRgFUS thalamotomy is more effective than sham treatment, but is associated with a risk of gait disturbance, paraesthesia and numbness.

TcMRgFUS thalamotomy for essential tremor compared with no treatment

Li et al (2019)'s modelling suggests that TcMRgFUS thalamotomy is a cost effective alternative to no treatment, with an ICER of £27,200 per QALY, within normal NHS value for money limits. However, the authors' utility estimates were derived from Herceg et al (2012), a study of drug treatment of essential tremor. Since this study was uncontrolled, the placebo effect may have exaggerated apparent treatment effects and therefore the utility gain from treatment. Furthermore, the authors' sensitivity analysis indicated that the ICER of TcMRgFUS thalamotomy versus no surgery was most sensitive to assumptions regarding baseline utility, underlining the importance of the issue mentioned above. In their base-case comparison of TcMRgFUS thalamotomy and no surgery, the authors disregarded the capital cost of TcMRgFUS thalamotomy equipment. Including it, a more realistic approach which reflects cost to the healthcare system, almost doubled the ICER to C$85,047 (£50,500) per QALY), beyond what is usually considered cost effective for the NHS in England. Canadian healthcare costs differ from those in the NHS, reducing the relevance of this analysis to the NHS. So this study does not support a conclusion that TcMRgFUS thalamotomy is cost effective enough for NHS use.

TcMRgFUS thalamotomy for essential tremor (no comparator)

Chang et al (2018) indicates that the effects of treatment reported by Elias et al (2016) are still present two years later, and suggests that late adverse effects do not emerge within this period of follow-up. However, discrepancies in Chang et al (2018)'s reporting cast doubt on the accuracy of the data reported in this study.

6 Conclusion

TcMRgFUS thalamotomy for essential tremor compared with DBS

TcMRgFUS thalamotomy may have advantages over DBS because it is less invasive, but there is no reliable evidence that either TcMRgFUS thalamotomy or DBS is safer or more effective than the other. Neither is there reliable, relevant evidence about the two procedures' relative cost-effectiveness.

TcMRgFUS thalamotomy for essential tremor compared with sham or no treatment

TcMRgFUS thalamotomy appears to be more effective than sham treatment, but is associated with a risk of gait disturbance, paraesthesia and numbness. The effects of treatment are still reportedly present two years later, with some adverse effects improving within this period of follow-up and no others emerging. The available evidence provides no reason to conclude that TcMRgFUS thalamotomy is cost effective enough for NHS use.

This evidence is consistent with NICE's recommendation that TcMRgFUS thalamotomy "should not be used unless there are special arrangements for clinical governance, consent, and audit or research."

7 Evidence Summary Tables

For abbreviations see list at end of tables

TcMRgFUS thalamotomy for essential tremor compared with DBS									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Li et al 2019	S2 Cost utility modelling	People with medically refractory disabling essential tremor	TcMRgFUS thalamotomy and no surgery in people ineligible for invasive neurosurgery. TcMRgFUS thalamotomy, DBS and radiofrequenc y thalamotomy[17] in people eligible for invasive neurosurgery.	Primary Incremental cost utility	Incremental cost effectiveness ratio (ICER)	DBS vs TcMRgFUS thalamotomy: incremental cost C$34,026 (£20,200), incremental utility 0.26 QALYs over 5 years, incremental cost utility C$130,850 (£77,700) per QALY	6	Direct	The authors assumed that TcMRgFUS thalamotomy and DBS are equally effective in tremor abatement but have different adverse event profiles. The authors' utility estimates were derived from Herceg et al (2012), a study of drug treatment of essential tremor. Since this study was uncontrolled, the placebo effect may have exaggerated the apparent treatment effects and therefore the utility gain from treatment. The ICER of DBS versus TcMRgFUS thalamotomy was sensitive to several assumptions related to DBS, including battery life, onset of benefit, risk of hardware complications, and risk of infection. However, none of the sensitivity analyses brought the cost within the usual affordability range. The authors do not report how capital costs of TcMRgFUS thalamotomy equipment was handled in this modelling; if it was excluded from the model, then adding it would decrease the incremental cost of DBS and improve its ICER. Canadian healthcare costs differ from those in the NHS, reducing the relevance of this analysis to the NHS.
Kim et al 2017	P1 Retrospe ctive unrando	59 "neurologica lly intact" people with essential	Unilateral TcMRgFUS thalamotomy (n=23, median age 65 years,	Primary Clinical effectiveness	Successful treatment[14] at one month	TcMRgFUS thalamotomy 21/23 (91%); DBS: 17/19 (89%); p-value not reported.	6	Direct	This study has a number of serious methodological weaknesses. Treatment allocation was not apparently concealed, so both participants and assessors may have been aware of which treatment was used, introducing potential bias. The method by

[17] Not reported here because radio-frequency ablation is out-of-scope

[14] Defined as absent tremor (complete remission) or occasional tremor (greater than 90% improvement) on the Fahn-Tolosa-Marin scale. This scale contains sections for assessing rest, postural and kinetic/intention tremor amplitude in specific anatomic locations (Part A), tremor in writing, drawing, and pouring (Part B), activities of daily living (Part C) and global assessments by the patient and examiner (Part D), with each item rated on a scale from 0 to 4. Higher scores indicate worse tremor.

TcMRgFUS thalamotomy for essential tremor compared with DBS									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
	mised controlled study. Patients reported here were treated between 2012 and 2014. Single centre, Seoul, Korea	tremor refractory to medical treatment and at least a year of follow-up.	20/23 (87%) male, median symptom duration 16 years (IQR 10 to 27 years)); unilateral DBS (n=19, median age 63 years, 13/19 (68%) male, median symptom duration 20 years (IQR 11 to 27 years)); unilateral radio-frequency ablation (n=17)[18].	Primary Clinical effectiveness	Complete remission at one month	TcMRgFUS thalamotomy 10/23 (43%); DBS: 6/19 (32%); p-value not reported.			which treatments were allocated was not reported, so patients with different prognoses may have been preferentially allocated to one or other treatment. The study was retrospective, and the authors do not report whether all eligible patients were included, introducing the possibility of further bias. Also, the authors do not report how many people were treated but not included because they were lost to follow-up; such patients may have had worse outcomes, introducing a further bias.
				Primary Clinical effectiveness	Successful treatment at twelve months	TcMRgFUS thalamotomy 18/23 (78%); DBS: 16/19 (84%); p-value not reported.			
				Primary Clinical effectiveness	Complete remission at twelve months	TcMRgFUS thalamotomy 8/23 (35%); DBS: 9/19 (47%); p-value not reported.			
				Primary Safety	Adverse effects	TcMRgFUS thalamotomy: mild facial paresis for first month after procedure 1/23 (4%); balance problems due to brain oedema for first month after procedure, controlled with oral steroid therapy plus mild facial paresis still present at 12 month 1/23 (4%). DBS: mild facial paresis for first month after procedure 1/19 (5%); balance problems relieved with stimulation adjustment 3/19 (16%); muscle twitching in the contralateral forearm 1/19 (5%).			

[18] Not reported here because radio-frequency ablation is out-of-scope

TcMRgFUS thalamotomy for essential tremor compared with DBS									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Ravikumar et al 2017	S2 Cost utility modelling	People with unilateral essential tremor	TcMRgFUS thalamotomy, DBS and stereotactic radiosurgery[19] for refractory essential tremor	Cost utility	Incremental cost effectiveness ratio	TcMRgFUS thalamotomy: cost US$20,593 (£16,140), QALYs (reported as "effectiveness") 0.194. DBS without staging: cost US$27,906 (£21,900), QALYs (reported as "effectiveness") 0.134. This implies that TcMRgFUS thalamotomy is dominant, being both more effective and less expensive.	2	Direct	The authors note that "Nearly all included reports represented uncontrolled observational studies and must be considered level 4 evidence". Nevertheless, the authors did not carry out individual critical appraisal of the reports of clinical effectiveness and safety on which they relied for estimates of clinical effectiveness, taking no account of the risk that the results were undermined by bias. They did not use any quality threshold for inclusion and report no sensitivity analysis to explore the effect of excluding lower quality papers. They do not report calculating the reports' heterogeneity before meta-analysing them. The authors use improvement in the disability section of the Clinical Rating Scale for Tremor (CRST)[20] as their measure of treatment effect. They claim that "It has been shown that this improvement can be mapped on a parametric measure of quality of life known as the utility score based on patient preference for a given health state". However, the reference that they cite in support of this (Martínez-Martín et al 2010) was a study to validate the Change in Quality of Life in Essential Tremor Questionnaire (QUEST)[21] and did not report an association between CRST and quality of life. This casts serious doubt on the extent to which a change in CRST score, even if accurately measured, could be used as a reliable estimate of the impact of treatment on quality of life. The authors intended to use US Medicare reimbursement costs for their model. However, "as Medicare reimbursement rates have not yet been determined for MRgFUS, these were estimated".

[19] Not reported here because stereotactic radiosurgery is out of scope

[20] The CRST is used to assess the severity of tremor. It has three parts: Part A (observed tremor), Part B (tasks) and Part C (disability), each scored from 0 to 4; higher scores indicate more severe tremor. Part A scores separately resting, postural, and action or intention components of hand tremor.

[21] Quality of Life in Essential Tremor Questionnaire (QUEST) includes 30 items in five domains (physical, psychosocial, communication, leisure and work/finance). Higher scores indicate lower quality of life.

TcMRgFUS thalamotomy for essential tremor compared with DBS									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
									The authors do not report how they were estimated. Since NHS costs differ substantially from those in the United States, and the US costs were not of demonstrable accuracy, there is substantial risk in using analysis based on these costs for NHS decision-making. The authors do not report what time horizon they used nor how they estimated the duration of life after treatment. They appear not to have discounted costs or benefits of treatment. Their reporting appears to confuse changes in CRST scores with quality-adjusted life years gained. Because of these serious methodological defects, little confidence can be placed in this study's results.
Huss et al 2015	P1 Retrospective unrandomised controlled study. Patients were treated between 2004 and 2013. Single neurosurgeon at a single centre in Charlottesville, USA	85 people with essential tremor refractory to medical treatment	Unilateral TcMRgFUS thalamotomy (n=15, mean age 67 years, 10/15 (67%) male, mean CRST score 64.4)); unilateral DBS (n=13, median age 72 years, 8/13 (62%) male, mean CRST score 59.5)); bilateral DBS (n=57, median age 63 years, 38/57 (67%) male, mean CRST score 54.9)).	Primary Clinical effectiveness	Change in CRST total score	Post-procedure score (percentage improvement from baseline): bilateral DBS 13.2 (79.5%); unilateral DBS 15.8 (62.8%); TcMRgFUS thalamotomy 17.7 (55.7%); all three procedures reported as improved versus baseline ($p<0.05$), and second two procedures reported as different from bilateral DBS ($p<0.05$).	4	Direct	This study has numerous serious methodological weaknesses. Treatment allocation was not apparently concealed, so both participants and assessors may have been aware of which treatment was used, introducing potential bias. The study was retrospective, and the authors do not report whether all eligible patients were included, introducing the possibility of further bias. Allocation to unilateral or bilateral DBS treatment depended on whether the participant had unilateral or bilateral tremor, though three participants with bilateral symptoms "chose not to have the second side treated after unilateral [DBS] placement", three "were recommended for unilateral treatment because of concerns regarding potential complications because of age and less cognitive reserve" and three others "had physical considerations (brain, skull, or scalp) that precluded bilateral treatment".
				Primary Clinical effectiveness	QUEST summary score	Mean pre- and post-procedure scores: bilateral DBS 52.1, 72.0;			

TcMRgFUS thalamotomy for essential tremor compared with DBS									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
			Mean follow up: unilateral TcMRgFUS thalamotomy 11.8 months, unilateral DBS 8.6 months, bilateral DBS 13.1 months, with no test of statistical significance reported. Median symptom duration not reported.			unilateral DBS not reported; TcMRgFUS thalamotomy 37.5, 68.0. Both post-procedure scores reported as improved versus baseline (p<0.05), but not showing different improvement between procedures.			The comparison is therefore potentially biased by the inclusion in the unilateral DBS group of patients with more extensive disease. This is corroborated by CRST scores indicating more severe disease in participants allocated to DBS. Similarly, the authors carried out 18 tests of statistical significance on their reported results of treatment, did not adjust the p-value and regarded as statistically significant those where p<0.05. Since they do not report p-values, we cannot tell which if any of these differences was significant with the correct, adjusted p-value of 0.00278[22]. Twelve patients, all treated with DBS, had “missing information or incomplete evaluations” and were excluded from the analysis. These patients may have had worse outcomes, introducing further bias. Since one participant with only three months of follow-up was included, it is unclear what the exclusion criteria were. Participants undergoing unilateral DBS had shorter follow-up, though the authors report no test of the significance of this difference. For patients who underwent DBS, postoperative evaluation took place 3 to 24 months (mean follow-up, 13 months) after the patient’s device was turned on. For patients who underwent TcMRgFUS thalamotomy, CRST was evaluated at 12 months after surgery, except for one patient who only had a 3-month follow-up. These differences in follow-up are further source of bias. Although higher QUEST scores indicate worse quality of life (confirmed by the authors (“QUEST summary index, (100% is worst)”), participants are reported as having higher QUEST scores after the procedures than before. Yet the authors report “After surgery, patients in both groups reported significant improvements in overall quality of life”. This
				Primary Clinical effectiveness	Proportion of participants with CRST tremor score of 2 to 4 in dominant hand pre-procedure who had a tremor score of 0 to 1 post-procedure	Bilateral DBS 46/55 (83.6%), unilateral DBS 11/13 (84.6%), TcMRgFUS thalamotomy 12/15 (80%), p>0.05.			
				Primary Clinical effectiveness	Proportion of participants with CRST handwriting score of 3 to 4 (illegible) pre-procedure who had a CRST handwriting score of 0 to 2 post-procedure	Bilateral DBS 20/26 (76.9%), unilateral DBS 7/8 (87.5%), TcMRgFUS thalamotomy 6/7 (86.7%), p>0.05.			
				Primary Safety	Adverse effects at 12 months	Bilateral DBS: paraesthesia 1/57 (1.8%), dysarthria 6/57 (11%), weakness 1/57 (1.8%), mental state change 3/57 (5.3%), hardware infection 1/57			

22 0.05/18

TcMRgFUS thalamotomy for essential tremor compared with DBS									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						(1.8%), lead erosion 2/57 (3.5%); unilateral DBS: paraesthesia 2/13 (15%); TcMRgFUS thalamotomy: paraesthesia 3/15 (20%); p-value not reported.			contradiction casts further doubt on the reliability of the paper. We have raised this issue with the authors, but have yet to receive a reply. For unilateral DBS procedures, "too few patients had preoperative and postoperative QUEST scores, so these patients were excluded from analysis of QUEST outcomes". Bilateral DBS results are of limited relevance to this RER, as TcMRgFUS thalamotomy was only used for patients with unilateral tremor.

TcMRgFUS thalamotomy for essential tremor compared with sham treatment									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Elias et al 2016	P1 Double-blind 3:1 randomised controlled trial with intention-to-treat analysis Eight centres	76 people with essential tremor refractory to two trials of medical treatment, a CRST tremor score of at least 2, and at least 2 on any of the eight items of the	TcMRgFUS thalamotomy (n=56, mean age 71 years, 33/56 (66%) male) Sham procedure (n=20, mean age 71 years, 15/20 (75%) male)	Primary Clinical effectiveness	Change in mean CRST hand tremor score[23] at 3 months	TcMRgFUS thalamotomy: pre-treatment 18.1, post-treatment 9.6 Sham: pre-treatment 16.0, post-treatment 15.8 Difference 8.3 points, 95% confidence interval (CI) 5.9 to 10.7, p<0.001.	9	Direct	This is a reliable randomised trial, which included independent analysis of videotapes by neurologists. Despite blinding, 95% of patients who underwent active treatment and 80% of those who underwent the sham procedure correctly guessed their assignment immediately after the procedure. However, the improvements are unlikely to be the result of chance or bias.
				Secondary Clinical effectiveness	Change in mean CRST hand tremor score at 12 months	TcMRgFUS thalamotomy: pre-treatment 18.1, post-treatment 10.9			

[23] This hand tremor score (on a scale ranging from 0 to 32, with higher scores indicating more severe tremor) was derived from the CRST, Part A (three items: resting, postural, and action or intention components of hand tremor), and the CRST, Part B (five tasks involving handwriting, drawing, and pouring), in the hand contralateral to the thalamotomy.

TcMRgFUS thalamotomy for essential tremor compared with sham treatment									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
	in USA, Canada, South Korea and Japan. Treatment in 2013 and 2014.	disability subsection of the CRST				Sham not reported. Difference 7.2 points, 95% CI 6.1 to 8.3, p<0.001.			
				Secondary Clinical effectiveness	Change in mean CRST disability score at 3 months	TcMRgFUS thalamotomy: pre-treatment 16.5, post-treatment 6.2; Sham: pre-treatment 16.0, post-treatment 15.6; Difference 9.9 points, p<0.001.			
				Secondary Clinical effectiveness	Change in mean QUEST score at 3 months	TcMRgFUS thalamotomy: pre-treatment 42.6, post-treatment 23.1 Sham: pre-treatment 42.8, post-treatment 41.1; Difference 17.8 points, p<0.001.			
				Secondary Safety	Adverse events	Gait disturbance (36%), paraesthesias or numbness (38%), persisting for 12 months in 9% and 14% of patients, respectively. One patient had dense and permanent hypaesthesia of the dominant thumb and index finger, categorised as a serious adverse event. One patient had a transient ischaemic attack 6 weeks after undergoing thalamotomy			

TcMRgFUS thalamotomy for essential tremor compared with no treatment									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
Li et al 2019	S2 Cost utility modelling	People with medically refractory disabling essential tremor	TcMRgFUS thalamotomy and no surgery in people ineligible for invasive neurosurgery. TcMRgFUS thalamotomy, DBS and radiofrequency thalamotomy[24] in people eligible for invasive neurosurgery.	Primary Incremental cost utility	Estimated cost per QALY	TcMRgFUS thalamotomy vs no surgery: incremental cost C$21,438 (£12,700), incremental utility 0.47 QALYs over 5 years, incremental cost utility $45,817 (£27,200) per QALY	6	Direct	Clinical effectiveness and safety results based on Elias et al 2016. The authors used age-specific background mortality for Ontario. Cost inputs were for Canada, and obtained from Ontario sources, published literature, clinical expert opinion and the manufacturer of MRgFUS device. The authors' utility estimates were derived from Herceg et al (2012), a study of drug treatment of essential tremor. Since this study was uncontrolled, the placebo effect may have exaggerated apparent treatment effects and therefore the utility gain from treatment.. The authors' sensitivity analysis indicated that the incremental cost-effectiveness (ICER) of TcMRgFUS thalamotomy versus no surgery was most sensitive to assumptions regarding baseline utility, underlining the importance of the issue in the paragraph above. In their base-case comparison of TcMRgFUS thalamotomy and no surgery, the authors disregarded the capital cost of TcMRgFUS thalamotomy equipment. Including it, a more realistic approach which reflects cost to the healthcare system, almost doubled the ICER to C$85,047 (£50,500) per QALY), beyond what is usually considered cost effective for the NHS. Canadian healthcare costs differ from those in the NHS, reducing the relevance of this analysis to the NHS in England.

[24] Not reported here because radio-frequency ablation is out-of-scope

TcMRgFUS thalamotomy for essential tremor (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Chang et al 2018	P1 Case series An uncontrolled 2-year follow-up of Elias et al 2016 Eight centres in USA, Canada, South Korea and Japan. Treatment in 2013 and 2014.	67 people with essential tremor refractory to two trials of medical treatment, a CRST tremor score of at least 2, and at least 2 on any of the eight items of the disability subsection of the CRST. 9/76 (12%) patients were either lost to follow-up, had alternative treatment or voluntarily withdrew from the study. The authors do not report demographic data on the 67 participants included in	TcMRgFUS thalamotomy	Primary Clinical effectiveness	Change in mean CRST hand tremor score[25] at 24 months	Pre-treatment 19.8; post-treatment 8.8; difference 11 points, 95% CI 7.6 to 10.0 points, p<0.001.	7	Direct	The authors report that "many" of the participants who were not followed-up "had unsuccessful treatment or suboptimal benefit". The exclusion of non-responders from the analysis introduces a bias and an overestimate of the benefit in those patients that remained in the study." Patients who did not attend follow-up for evaluation at 2 years postoperatively were analysed using the last observation carried forward method. Elias et al 2016 reported mean pre-treatment hand tremor scores derived from CRST Parts A and B of 18.1 in the TcMRgFUS thalamotomy group and 16 in the sham group. Chang et al 2018 reports a mean pre-treatment hand tremor score derived in the same way from all 76 participants of 19.8, higher than in either of the constituent groups. Furthermore, the authors' reported 95% CIs for changes in CRST scores do not include the reported value for this parameter. These discrepancies cast doubt on the accuracy of the data reported in this study. The authors do not report QUEST data in this paper, and do not explain its absence. Both the posture and action components of CRST Part A showed improvement.
				Primary Clinical effectiveness	Change in mean CRST disability score[26] at 24 months	Pre-treatment 16.4; post-treatment 6.5; difference 9.9 points, 95% CI 5.3 to 7.7 points, p<0.001.			
				Secondary Safety	Adverse events	None of the adverse events reported in Elias et al 2016 worsened at 2 years follow-up, and 2 of these events resolved (dysergia and paraesthesia). There were no new adverse events in the participants reported during the second year of follow-up.			

[25] The tremor score (on a scale ranging from 0 to 32, with higher scores indicating more severe tremor) was derived from the CRST Part A (three items: resting, postural, and action or intention components of hand tremor), and the CRST Part B (five tasks involving handwriting, drawing, and pouring), in the hand contralateral to the thalamotomy.

[26] Derived from CRST Part C

TcMRgFUS thalamotomy for essential tremor (no comparator)									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
		this study, nor on those who withdrew.							

Abbreviations

CRST: Clinical Rating Scale for Tremor. DBS: deep brain stimulation. ICER: incremental cost-effectiveness ratio. QALY: quality-adjusted life year. TcMRgFUS: trans-cranial magnetic resonance-guided focused ultrasound

8 Grade of Evidence Tables

For abbreviations see list at end of tables

TcMRgFUS thalamotomy for essential tremor compared with DBS					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Incremental cost effectiveness ratio	Li et al 2019	6	Direct	C	An incremental cost effectiveness ratio (ICER) is the ratio of the extra costs of an intervention, above that of alternatives, to the extra benefits it provides. Li et al 2019 report DBS vs TcMRgFUS thalamotomy to have an incremental cost of C$34,026 (£20,200), incremental utility of 0.26 quality-adjusted life years (QALYs) over 5 years and an incremental cost utility C$130,850 (£77,700) per QALY, above normal NHS value for money limits. A lower incremental cost effectiveness ratio indicates better value for money. This does not directly benefit individual patients, but means that more patients can be treated with the resources available. This study appears to suggest that DBS is not a cost effective alternative to TcMRgFUS thalamotomy. However, this conclusion rests on potentially unsound foundations. Li et al's cost inputs were for Canada, and obtained from Ontario sources, published literature, clinical expert opinion and the manufacturer of MRgFUS device. The authors' utility estimates were derived from Herceg et al (2012), a study of drug treatment of essential tremor. Since this study was uncontrolled, the placebo effect may have exaggerated apparent treatment effects and therefore the utility gain from treatment. The ICER of DBS versus TcMRgFUS thalamotomy was sensitive to several assumptions related to DBS, including battery life, onset of benefit, risk of hardware complications, and risk of infection. However, none of the sensitivity analyses brought the cost within the usual affordability range. The authors do not report how capital costs of TcMRgFUS thalamotomy equipment was handled in this modelling; if it was excluded from the model, then adding it would decrease the incremental cost of DBS and improve its ICER. Canadian healthcare costs differ from those in the NHS, reducing the relevance of this analysis to the NHS.
	Ravikumar et al 2017	2	Direct		
Successful treatment at one month	Kim et al 2017	6	Direct	C	The authors defined successful treatment as absent tremor (complete remission) or occasional tremor (greater than 90% improvement) on the Fahn-Tolosa-Marin scale[27]. Kim et al 2017 report rates of successful treatment at one month of 21/23 (91%) after TcMRgFUS thalamotomy and 17/19 (89%) after DBS (no p-value reported). Successful treatment would be of high value to patients. This study has a number of serious methodological weaknesses. Treatment allocation was not apparently concealed, so both participants and assessors may have been aware of which treatment was used, introducing potential bias. The method by which treatments were allocated was not reported, so patients with different prognoses may

[27] This scale contains sections for assessing rest, postural and kinetic/ intention tremor amplitude in specific anatomic locations (part A), tremor in writing, drawing, and pouring (part B), activities of daily living (part C), and global assessments by the patient and examiner (part D), with each item rated on a scale from 0 to 4. Higher scores indicate worse tremor.

TcMRgFUS thalamotomy for essential tremor compared with DBS					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					have been preferentially allocated to one or other treatment. The study was retrospective, and the authors do not report whether all eligible patients were included, introducing the possibility of further bias. Also, the authors do not report how many people were treated but not included because they were lost to follow-up; such patients may have had worse outcomes, introducing a further bias. The results are therefore of limited value.
Complete remission at one month	Kim et al 2017	6	Direct	C	The authors defined complete remission as absent tremor. Kim et al 2017 report rates of complete remission at one month of 10/23 (43%) after TcMRgFUS thalamotomy and 6/19 (32%) after DBS (no p-value reported). Complete remission would be of very high value to patients. This study has a number of serious methodological weaknesses. Treatment allocation was not apparently concealed, so both participants and assessors may have been aware of which treatment was used, introducing potential bias. The method by which treatments were allocated was not reported, so patients with different prognoses may have been preferentially allocated to one or other treatment. The study was retrospective, and the authors do not report whether all eligible patients were included, introducing the possibility of further bias. Also, the authors do not report how many people were treated but not included because they were lost to follow-up; such patients may have had worse outcomes, introducing a further bias. The results are therefore of limited value.
Successful treatment at twelve months	Kim et al 2017	6	Direct	C	The authors defined successful treatment as absent tremor (complete remission) or occasional tremor (greater than 90% improvement) on the Fahn-Tolosa-Marin scale[28]. Kim et al 2017 report rates of successful treatment at twelve months of 18/23 (78%) after TcMRgFUS thalamotomy and 16/19 (84%) after DBS, (no p-value reported). Successful treatment would be of high value to patients. This study has a number of serious methodological weaknesses. Treatment allocation was not apparently concealed, so both participants and assessors may have been aware of which treatment was used, introducing potential bias. The method by which treatments were allocated was not reported, so patients with different prognoses may have been preferentially allocated to one or other treatment. The study was retrospective, and the authors do not report whether all eligible patients were included, introducing the possibility of further bias. Also, the authors do not report how many people were treated but not included because they were lost to follow-up; such patients may have had worse outcomes, introducing a further bias. The results are therefore of limited value.
Complete remission at twelve months	Kim et al 2017	6	Direct	C	The authors defined complete remission as absent tremor.

[28] This scale contains sections for assessing rest, postural and kinetic/ intention tremor amplitude in specific anatomic locations (part A); tremor in writing, drawing, and pouring (part B); activities of daily living (part C); and global assessments by the patient and examiner, with each item rated on a scale from 0 to 4. Higher scores indicate worse tremor.

TcMRgFUS thalamotomy for essential tremor compared with DBS					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					Kim et al 2017 report rates of complete remission at twelve months of 8/23 (35%) after TcMRgFUS thalamotomy and 9/19 (32%) after DBS (no p-value reported). Complete remission would be of very high value to patients. This study has a number of serious methodological weaknesses. Treatment allocation was not apparently concealed, so both participants and assessors may have been aware of which treatment was used, introducing potential bias. The method by which treatments were allocated was not reported, so patients with different prognoses may have been preferentially allocated to one or other treatment. The study was retrospective, and the authors do not report whether all eligible patients were included, introducing the possibility of further bias. Also, the authors do not report how many people were treated but not included because they were lost to follow-up; such patients may have had worse outcomes, introducing a further bias. The results are therefore of limited value.
Adverse effects	Kim et al 2017	6	Direct	B	Adverse effects are unwanted or harmful results of treatment. Kim et al 2017 report the following adverse effects: TcMRgFUS thalamotomy: mild facial paresis for first month after procedure: 1/23 (4%); balance problems due to brain oedema for first month after procedure, controlled with oral steroid therapy plus mild facial paresis still present at 12 month 1/23 (4%). DBS: mild facial paresis for first month after procedure: 1/19 (5%); balance problems relieved with stimulation adjustment 3/19 (16%); muscle twitching in the contralateral forearm 1/19 (5%). Avoiding adverse effects is of high value to patients. Kim et al 2017 has a number of serious methodological weaknesses. Treatment allocation was not apparently concealed, so both participants and assessors may have been aware of which treatment was used, introducing potential bias. The method by which treatments were allocated was not reported, so patients with different prognoses may have been preferentially allocated to one or other treatment. The study was retrospective, and the authors do not report whether all eligible patients were included, introducing the possibility of further bias. Also, the authors do not report how many people were treated but not included because they were lost to follow-up; such patients may have had worse outcomes, introducing a further bias. The results are therefore of limited value.
	Huss et al 2015	4	Direct		
Change in CRST total score	Huss et al 2015	4	Direct	C	The Clinical Rating Scale for Tremor (CRST) scale is used to assess the severity of tremor. It has three parts: Part A (observed tremor), Part B (tasks) and Part C (disability), each scored from 0 to 4; higher scores indicate more severe tremor. Part A separately scores resting, postural, and action or intention components of hand tremor. Huss et al 2015 report the following post-procedure scores (percentage improvement from baseline): bilateral DBS 13.2 (79.5%); unilateral DBS 15.8 (62.8%); TcMRgFUS thalamotomy 17.7 (55.7%). All three procedures are reported as improved versus baseline ($p<0.05$), and the second two procedures are reported as different from bilateral DBS ($p<0.05$).

TcMRgFUS thalamotomy for essential tremor compared with DBS					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					Improvement in tremor would be of high value to patients. However, this study has numerous serious methodological weaknesses. Treatment allocation was not apparently concealed, so both participants and assessors may have been aware of which treatment was used, introducing potential bias. The study was retrospective, and the authors do not report whether all eligible patients were included, introducing the possibility of further bias. Allocation to unilateral or bilateral DBS treatment depended on whether the participant had unilateral or bilateral tremor, though three participants with bilateral symptoms "chose not to have the second side treated after unilateral [DBS] placement", three "were recommended for unilateral treatment because of concerns regarding potential complications because of age and less cognitive reserve" and three others "had physical considerations (brain, skull, or scalp) that precluded bilateral treatment". The comparison is therefore potentially biased by the inclusion in the TcMRgFUS thalamotomy group of patients with less extensive disease. This is corroborated by CRST scores indicating more severe disease in participants allocated to DBS. Similarly, the authors carried out 18 tests of statistical significance on their reported results of treatment, did not adjust the p-value and regarded as statistically significant those where $p<0.05$. Since they do not report p-values, we cannot tell which if any of these differences was significant with the correct, adjusted p-value of 0.00278. Twelve patients, all treated with DBS, had "missing information or incomplete evaluations" and were excluded from the analysis. These patients may have had worse outcomes, introducing further bias. Since one participant with only three months of follow-up was included, it is unclear what the exclusion criteria were. Participants undergoing unilateral DBS had shorter follow-up, though the authors report no test of the significance of this difference. For patients who underwent DBS, postoperative evaluation took place 3 to 24 months (mean follow-up, 13 months) after the patient's device was turned on. For patients who underwent TcMRgFUS thalamotomy, CRST was evaluated at 12 months after surgery, except for one patient who only had a 3-month follow-up. These differences in follow-up are further source of bias. Although higher QUEST scores indicate worse quality of life (confirmed by the authors ("QUEST summary index, (100% is worst)"), participants are reported as having higher QUEST scores after the procedures than before. Yet the authors report "After surgery, patients in both groups reported significant improvements in overall quality of life". This contradiction casts further doubt on the reliability of the paper. We raised this issue with the authors, but have received no reply. For unilateral DBS procedures, "too few patients had preoperative and postoperative QUEST scores, so these patients were excluded from analysis of QUEST outcomes". Bilateral DBS results are of limited relevance to this RER, as TcMRgFUS thalamotomy was only used for patients with unilateral tremor.
QUEST summary score	Huss et al 2015	4	Direct	C	The Quality of Life in Essential Tremor Questionnaire (QUEST) includes 30 items in five domains (physical, psychosocial, communication, leisure and work/finance). Higher scores indicate lower quality of life. Huss et al 2015 report the following mean pre- and post-procedure scores: bilateral DBS 52.1, 72.0; unilateral DBS not reported; TcMRgFUS thalamotomy 37.5, 17.7. Both post-procedure scores reported as improved versus baseline ($p<0.05$), but not showing different improvement between procedures.

TcMRgFUS thalamotomy for essential tremor compared with DBS					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					Improvement in quality of life would be of very high value to patients. However, this study has numerous serious methodological weaknesses. Treatment allocation was not apparently concealed, so both participants and assessors may have been aware of which treatment was used, introducing potential bias. The study was retrospective, and the authors do not report whether all eligible patients were included, introducing the possibility of further bias. Allocation to unilateral or bilateral DBS treatment depended on whether the participant had unilateral or bilateral tremor, though three participants with bilateral symptoms “chose not to have the second side treated after unilateral [DBS] placement”, three “were recommended for unilateral treatment because of concerns regarding potential complications because of age and less cognitive reserve” and three others “had physical considerations (brain, skull, or scalp) that precluded bilateral treatment”. The comparison is therefore potentially biased by the inclusion in the TcMRgFUS thalamotomy group of patients with less extensive disease. This is corroborated by CRST scores indicating more severe disease in participants allocated to DBS. Similarly, the authors carried out 18 tests of statistical significance on their reported results of treatment, did not adjust the p-value and regarded as statistically significant those where $p<0.05$. Since they do not report p-values, we cannot tell which if any of these differences was significant with the correct, adjusted p-value of 0.00278. Twelve patients, all treated with DBS, had “missing information or incomplete evaluations” and were excluded from the analysis. These patients may have had worse outcomes, introducing further bias. Since one participant with only three months of follow-up was included, it is unclear what the exclusion criteria were. Participants undergoing unilateral DBS had shorter follow-up, though the authors report no test of the significance of this difference. For patients who underwent DBS, postoperative evaluation took place 3 to 24 months (mean follow-up, 13 months) after the patient’s device was turned on. For patients who underwent TcMRgFUS thalamotomy, CRST was evaluated at 12 months after surgery, except for one patient who only had a 3-month follow-up. These differences in follow-up are further source of bias. Although higher QUEST scores indicate worse quality of life (confirmed by the authors (“QUEST summary index, (100% is worst)”), participants are reported as having higher QUEST scores after the procedures than before. Yet the authors report “After surgery, patients in both groups reported significant improvements in overall quality of life”. This contradiction casts further doubt on the reliability of the paper. We raised this issue with the authors, but received no reply. For unilateral DBS procedures, “too few patients had preoperative and postoperative QUEST scores, so these patients were excluded from analysis of QUEST outcomes”. Bilateral DBS results are of limited relevance to this RER, as TcMRgFUS thalamotomy was only used for patients with unilateral tremor.
Proportion of participants with CRST handwriting score of 2 to 4 in dominant hand pre-procedure who had a tremor score of 0 to 1 post-procedure	Huss et al 2015	4	Direct	C	This outcome covers the proportion of participants reporting a degree of improvement in handwriting. Huss et al 2015 report the following post-procedure scores (percentage improvement from baseline): bilateral DBS 46/55 (83.6%), unilateral DBS 11/13 (84.6%), TcMRgFUS thalamotomy 12/15 (80%). The differences between these proportions are reported as not statistically significant.

TcMRgFUS thalamotomy for essential tremor compared with DBS					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					Improvement in handwriting would be of value to patients. However, this study has numerous serious methodological weaknesses. Treatment allocation was not apparently concealed, so both participants and assessors may have been aware of which treatment was used, introducing potential bias. The study was retrospective, and the authors do not report whether all eligible patients were included, introducing the possibility of further bias. Allocation to unilateral or bilateral DBS treatment depended on whether the participant had unilateral or bilateral tremor, though three participants with bilateral symptoms "chose not to have the second side treated after unilateral [DBS] placement", three "were recommended for unilateral treatment because of concerns regarding potential complications because of age and less cognitive reserve" and three others "had physical considerations (brain, skull, or scalp) that precluded bilateral treatment". The comparison is therefore potentially biased by the inclusion in the TcMRgFUS thalamotomy group of patients with less extensive disease. This is corroborated by CRST scores indicating more severe disease in participants allocated to DBS. Similarly, the authors carried out 18 tests of statistical significance on their reported results of treatment, did not adjust the p-value and regarded as statistically significant those where $p<0.05$. Since they do not report p-values, we cannot tell which if any of these differences was significant with the correct, adjusted p-value of 0.00278. Twelve patients, all treated with DBS, had "missing information or incomplete evaluations" and were excluded from the analysis. These patients may have had worse outcomes, introducing further bias. Since one participant with only three months of follow-up was included, it is unclear what the exclusion criteria were. Participants undergoing unilateral DBS had shorter follow-up, though the authors report no test of the significance of this difference. For patients who underwent DBS, postoperative evaluation took place 3 to 24 months (mean follow-up, 13 months) after the patient's device was turned on. For patients who underwent TcMRgFUS thalamotomy, CRST was evaluated at 12 months after surgery, except for one patient who only had a 3-month follow-up. These differences in follow-up are further source of bias. Although higher QUEST scores indicate worse quality of life (confirmed by the authors ("QUEST summary index, (100% is worst)"), participants are reported as having higher QUEST scores after the procedures than before. Yet the authors report "After surgery, patients in both groups reported significant improvements in overall quality of life". This contradiction casts further doubt on the reliability of the paper. We raised this issue with the authors, but received no reply. For unilateral DBS procedures, "too few patients had preoperative and postoperative QUEST scores, so these patients were excluded from analysis of QUEST outcomes". Bilateral DBS results are of limited relevance to this RER, as TcMRgFUS thalamotomy was only used for patients with unilateral tremor.
Proportion of participants with CRST handwriting score of 3 or 4 (illegible) pre-procedure who had a tremor score of 0 to 2 post-procedure	Huss et al 2015	4	Direct	C	This outcome covers the proportion of participants reporting a degree of improvement in handwriting. Huss et al 2015 report the following post-procedure scores (percentage improvement from baseline): bilateral DBS 20/26 (76.9%), unilateral DBS 7/8 (87.5%), TcMRgFUS thalamotomy 6/7 (86.7%), The differences between these proportions are reported as not statistically significant.

TcMRgFUS thalamotomy for essential tremor compared with DBS					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					Improvement in handwriting would be of value to patients. However, this study has numerous serious methodological weaknesses. Treatment allocation was not apparently concealed, so both participants and assessors may have been aware of which treatment was used, introducing potential bias. The study was retrospective, and the authors do not report whether all eligible patients were included, introducing the possibility of further bias. Allocation to unilateral or bilateral DBS treatment depended on whether the participant had unilateral or bilateral tremor, though three participants with bilateral symptoms “chose not to have the second side treated after unilateral [DBS] placement”, three “were recommended for unilateral treatment because of concerns regarding potential complications because of age and less cognitive reserve” and three others “had physical considerations (brain, skull, or scalp) that precluded bilateral treatment”. The comparison is therefore potentially biased by the inclusion in the TcMRgFUS thalamotomy group of patients with less extensive disease. This is corroborated by CRST scores indicating more severe disease in participants allocated to DBS. Similarly, the authors carried out 18 tests of statistical significance on their reported results of treatment, did not adjust the p-value and regarded as statistically significant those where $p<0.05$. Since they do not report p-values, we cannot tell which if any of these differences was significant with the correct, adjusted p-value of 0.00278. Twelve patients, all treated with DBS, had “missing information or incomplete evaluations” and were excluded from the analysis. These patients may have had worse outcomes, introducing further bias. Since one participant with only three months of follow-up was included, it is unclear what the exclusion criteria were. Participants undergoing unilateral DBS had shorter follow-up, though the authors report no test of the significance of this difference. For patients who underwent DBS, postoperative evaluation took place 3 to 24 months (mean follow-up, 13 months) after the patient’s device was turned on. For patients who underwent TcMRgFUS thalamotomy, CRST was evaluated at 12 months after surgery, except for one patient who only had a 3-month follow-up. These differences in follow-up are further source of bias. Although higher QUEST scores indicate worse quality of life (confirmed by the authors (“QUEST summary index, (100% is worst)”), participants are reported as having higher QUEST scores after the procedures than before. Yet the authors report “After surgery, patients in both groups reported significant improvements in overall quality of life”. This contradiction casts further doubt on the reliability of the paper. We raised this issue with the authors, but received no reply For unilateral DBS procedures, “too few patients had preoperative and postoperative QUEST scores, so these patients were excluded from analysis of QUEST outcomes”. Bilateral DBS results are of limited relevance to this RER, as TcMRgFUS thalamotomy was only used for patients with unilateral tremor.

TcMRgFUS thalamotomy for essential tremor compared with sham treatment					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Change in mean CRST hand tremor score[29] at 3 months	Elias et al 2016	9	Direct	B	This hand tremor score (on a scale ranging from 0 to 32, with higher scores indicating more severe tremor) was derived from the CRST, Part A (three items: resting, postural, and action or intention components of hand tremor), and the CRST, Part B (five tasks involving handwriting, drawing, and pouring), in the hand contralateral to the thalamotomy. Elias et al 2016 report the following results: TcMRgFUS thalamotomy: pre-treatment 18.1, post-treatment 9.6; sham pre-treatment 16.0, post-treatment 15.8; difference 8.3 points, 95% confidence interval (CI) 5.9 to 10.7, p<0.001. Improvement in hand tremor would be of high value to patients. This is a reliable randomised trial, which included independent analysis of videotapes by neurologists. Despite blinding, 95% of patients who underwent active treatment and 80% of those who underwent the sham procedure correctly guessed their assignment immediately after the procedure. However, the improvements are unlikely to be the result of chance or bias.
Change in mean CRST hand tremor score at 12 months	Elias et al 2016	9	Direct	B	This hand tremor score (on a scale ranging from 0 to 32, with higher scores indicating more severe tremor) was derived from the CRST, Part A (three items: resting, postural, and action or intention components of hand tremor), and the CRST, Part B (five tasks involving handwriting, drawing, and pouring), in the hand contralateral to the thalamotomy. Elias et al 2016 report the following results: TcMRgFUS thalamotomy: pre-treatment 18.1, post-treatment 10.9; sham not reported; difference between treatments 7.2 points, 95% CI 6.1 to 8.3, p<0.001. Improvement in hand tremor would be of high value to patients. This is a reliable randomised trial, which included independent analysis of videotapes by neurologists. Despite blinding, 95% of patients who underwent active treatment and 80% of those who underwent the sham procedure correctly guessed their assignment immediately after the procedure. However, the improvements are unlikely to be the result of chance or bias.
Change in mean CRST disability score at 3 months	Elias et al 2016	9	Direct	B	The CRST disability score is derived from Part C of CRST, which measures functional disability. Elias et al 2016 report the following results: TcMRgFUS thalamotomy: pre-treatment 16.5, post-treatment 6.2; sham pre-treatment 16.0, post-treatment 15.6; difference 9.9 points, p<0.001. Improvement in disability would be of high value to patients.

[29] The tremor score (on a scale ranging from 0 to 32, with higher scores indicating more severe tremor) was derived from the CRST, Part A (three items: resting, postural, and action or intention components of hand tremor), and the CRST, Part B (five tasks involving handwriting, drawing, and pouring), in the hand contralateral to the thalamotomy.

TcMRgFUS thalamotomy for essential tremor compared with sham treatment					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					This is a reliable randomised trial, which included independent analysis of videotapes by neurologists. Despite blinding, 95% of patients who underwent active treatment and 80% of those who underwent the sham procedure correctly guessed their assignment immediately after the procedure. However, the improvements are unlikely to be the result of chance or bias.
Change in mean QUEST score at 3 months	Elias et al 2016	9	Direct	B	The Quality of Life in Essential Tremor Questionnaire (QUEST) includes 30 items in five domains (physical, psychosocial, communication, leisure and work/finance). Higher scores indicate lower quality of life. Elias et al 2016 report the following results: TcMRgFUS thalamotomy: pre-treatment 42.6, post-treatment 23.1; sham pre-treatment 42.8, post-treatment 41.1; difference 17.8 points, p<0.001. Improvement in quality of life would be of very high value to patients. This is a reliable randomised trial, which included independent analysis of videotapes by neurologists. Despite blinding, 95% of patients who underwent active treatment and 80% of those who underwent the sham procedure correctly guessed their assignment immediately after the procedure. However, the improvements are unlikely to be the result of chance or bias.
Adverse effects	Elias et al 2016	9	Direct	B	Adverse effects are unwanted or harmful results of treatment. Elias et al 2016 report the following adverse effects of TcMRgFUS thalamotomy: gait disturbance (36%), paraesthesias or numbness (38%), persisting for 12 months in 9% and 14% of patients, respectively. One patient had dense and permanent hypaesthesia of the dominant thumb and index finger, categorised as a serious adverse event. One patient had a transient ischaemic attack 6 weeks after undergoing thalamotomy. Avoiding adverse effects is of high value to patients. This is a reliable randomised trial, which included independent analysis of videotapes by neurologists. Despite blinding, 95% of patients who underwent active treatment and 80% of those who underwent the sham procedure correctly guessed their assignment immediately after the procedure. However, the improvements are unlikely to be the result of chance or bias.

TcMRgFUS thalamotomy for essential tremor compared with no treatment					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Incremental cost effectiveness ratio	Li et al 2019	6	Direct	C	An incremental cost effectiveness ratio (ICER) is the ratio of the extra costs of an intervention, above that of alternatives, to the extra benefits it provides. Li et al 2019 report TcMRgFUS thalamotomy vs no treatment to have an incremental cost of C$21,438 (£12,700), incremental utility of 0.47 QALYs over 5 years and an incremental cost utility $45,817 (£27,200) per QALY, within normal NHS value for money limits. A lower incremental cost effectiveness ratio indicates better value for money. This does not directly benefit individual patients, but means that more patients can be treated with the resources available. This study appears to suggest that TcMRgFUS thalamotomy is a cost effective alternative to no treatment. However, this conclusion rests on potentially unsound foundations. Li et al's cost inputs were for Canada, and obtained from Ontario sources, published literature, clinical expert opinion and the manufacturer of MRgFUS device. The authors' utility estimates were derived from Herceg et al (2012), a study of drug treatment of essential tremor. Since this study was uncontrolled, the placebo effect may have exaggerated apparent treatment effects and therefore the utility gain from treatment. The authors' sensitivity analysis indicated that the incremental cost-effectiveness (ICER) of TcMRgFUS thalamotomy versus no surgery was most sensitive to assumptions regarding baseline utility, underlining the importance of this issue. In their base-case comparison of TcMRgFUS thalamotomy and no surgery, the authors disregarded the capital cost of TcMRgFUS thalamotomy equipment. Including it, a more realistic approach which reflects cost to the healthcare system, almost doubled the ICER to C$85,047 (£50,500) per QALY), beyond what is considered value for NHS money. Canadian healthcare costs differ from those in the NHS, reducing the relevance of this analysis to the NHS.

TcMRgFUS thalamotomy for essential tremor (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Change in mean CRST hand tremor score at 24 months	Chang et al 2018	7	Direct	B	This hand tremor score (on a scale ranging from 0 to 32, with higher scores indicating more severe tremor) was derived from the CRST, Part A (three items: resting, postural, and action or intention components of hand tremor), and the CRST, Part B (five tasks involving handwriting, drawing, and pouring), in the hand contralateral to the thalamotomy. Chang et al 2018 report the following results: pre-treatment 19.8; post-treatment 8.8; difference 11 points, 95% CI 7.6 to 10.0 points, p<0.001. Improvement in hand tremor would be of high value to patients. There are concerns about the reliability of this study. The authors report that “many” of the participants who were not followed-up “had unsuccessful treatment or suboptimal benefit”. The exclusion of non-responders from the analysis introduces a bias and an overestimate of the benefit in those patients that remained in the study.” Elias et al 2016 reported mean pre-treatment hand tremor scores derived from CRST Parts A and B of 18.1 in the TcMRgFUS thalamotomy group and 16 in the sham group. Chang et al 2018 reports a mean pre-treatment hand tremor score derived in the same way from all 76 participants of 19.8, higher than in either of the constituent groups. Furthermore, the authors’ reported 95% CIs for changes in CRST scores do not include the reported value for this parameter. These discrepancies cast doubt on the accuracy of the data reported in this study.
Change in mean CRST disability score at 24 months	Chang et al 2018	7	Direct	B	This disability score was derived from the CRST Part C. Chang et al 2018 report the following results: pre-treatment 16.4; post-treatment 6.5; difference 9.9 points, 95% CI 5.3 to 7.7 points, p<0.001. Improvement in disability would be of high value to patients. There are concerns about the reliability of this study. The authors report that “many” of the participants who were not followed-up “had unsuccessful treatment or suboptimal benefit”. The exclusion of non-responders from the analysis introduces a bias and an overestimate of the benefit in those patients that remained in the study.” Elias et al 2016 reported mean pre-treatment hand tremor scores derived from CRST Parts A and B of 18.1 in the TcMRgFUS thalamotomy group and 16 in the sham group. Chang et al 2018 reports a mean pre-treatment hand tremor score derived in the same way from all 76 participants of 19.8, higher than in either of the constituent groups. Furthermore, the authors’ reported 95% CIs for changes in CRST scores do not include the reported value for this parameter. These discrepancies cast doubt on the accuracy of the data reported in this study.

TcMRgFUS thalamotomy for essential tremor (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Adverse events	Chang et al 2018	7	Direct	B	Adverse effects are unwanted or harmful results of treatment. Chang et al 2018 report that none of the adverse events reported in Elias et al 2016 worsened at 2 years follow-up, and 2 of these events resolved (dysergia and paraesthesia). There were no new adverse events in the participants reported during the second year of follow-up. Avoiding adverse effects is of high value to patients. There are concerns about the reliability of this study. The authors report that “many” of the participants who were not followed-up “had unsuccessful treatment or suboptimal benefit”. The exclusion of non-responders from the analysis introduces a bias and an overestimate of the benefit in those patients that remained in the study.” Elias et al 2016 reported mean pre-treatment hand tremor scores derived from CRST Parts A and B of 18.1 in the TcMRgFUS thalamotomy group and 16 in the sham group. Chang et al 2018 reports a mean pre-treatment hand tremor score derived in the same way from all 76 participants of 19.8, higher than in either of the constituent groups. Furthermore, the authors’ reported 95% CIs for changes in CRST scores do not include the reported value for this parameter. These discrepancies cast doubt on the accuracy of the data reported in this study.

CRST: Clinical Rating Scale for Tremor. DBS: deep brain stimulation. ICER: incremental cost-effectiveness ratio. QALY: quality-adjusted life year. TcMRgFUS: trans-cranial magnetic resonance-guided focused ultrasound

9 Literature Search Terms

PICO Table[30]	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Adults aged 18 years and above with treatment (medication)-refractory (resistant) essential tremor • Subgroup: varying levels of severity (for example: mild, moderate and severe tremor based on CRST (see below in outcomes)
I – Intervention Which intervention, treatment or approach should be used?	Unilateral transcranial MRI-guided focussed ultrasound (TcMRgFUS) thalamotomy {Alternative terms for information: brain-High Intensity focused ultrasound; Brain-Focused ultrasound)
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	1. Conservative management (i.e. no treatment beyond drug therapy; to include "sham" procedures) 2. Deep Brain Stimulation (DBS)[31]
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	<u>*Critical to decision-making:*</u> • Efficacy: o Improvement in Tremor severity scale (including, but not limited to: Clinical Rating Scale for Tremor[32]) o Improvement in disability and activity of disability scales o Improvement in quality of life scales (including, but not limited to: Quality of Life in Essential Tremor Scale Questionnaire[33] • Safety o Complications[34] o Mortality <u>*Important to decision-making:*</u> • Length of stay • Re-admission • Cost-effectiveness • Patient assessed treatment acceptability
Assumptions / limits applied to search	
Inclusions	
Study design:	Systematic reviews, randomised controlled trials, controlled clinical trials, comparative cohort studies. If no higher-level quality evidence is found, case series can be considered
Language:	English only
Patients:	Human studies only
Age:	18 years and above.
Date limits:	2009 – 2019

[30] The footnotes for this table are the notes that were attached to this PICO table supplied by NHS England.
[31] Stereotactic radiosurgery (SRS) and radiofrequency ablation (RFA) are different treatment options for essential tremor that are not used in current practice. Therefore, they have been excluded from the search.
[32] Clinical Rating Scale for Tremor (CRST) is the most widely used clinical rating scale for tremor and has been approved by the International Movement Disorder Society Task Force on Tremor – Tremor Measurement Group. The scoring system consists of three components

- Rest, postural and kinetic tremor amplitude in specific anatomic locations (impairment),
- Tremor in writing, drawing and pouring (disability),
- Activities of daily living (disability and social handicap)

[33] The Quality of Life in Essential Tremor scale Questionnaire (QUEST) is specifically designed for essential tremor which consists of rating 30 items on a five-point scale with domains including physical, psychosocial, communication, leisure and work/finance components.
[34] Complications that may be encountered in the literature may include, but are not limited to: intraoperative complications, immediate complications post-procedure, dysarthria, paraesthesia, gait/balance disturbance, intracranial haemorrhage, stroke,

Exclusions	
Publication Type:	Conference abstracts, narrative reviews, commentaries, letters and editorials
Study design:	Case reports, resource utilisation studies

10 Search Strategy

We searched PubMed, Embase and Cochrane Library limiting the search to papers published in English from 1st January 2009 to 15th May 2019. We excluded commentary, letters, editorials, review articles, conference abstracts and case reports.

Embase search:

1	Essential Tremor/
2	((essential or refractory) adj3 tremor?).ti,ab.
3	tremor?.ti.
4	1 or 2 or 3
5	interventional ultrasonography/
6	high intensity focused ultrasound/ or mr-guided focused ultrasound/
7	(((high intensity or focused) adj3 (ultrasonogra* or ultrasound? or ultra-sonogra* or ultra-soun sonogra*)) or hifu).ti,ab.
8	tcmrgfus.ti,ab.
9	ultrasound therapy/
10	ultrasound/
11	di.fs.
12	(ultrasonogra* or ultrasound? or ultra-sonogra* or ultra-sound* or sonogra*).ti,ab.
13	9 or 10 or 11 or 12
14	nuclear magnetic resonance imaging/ or nuclear magnetic resonance/
15	interventional magnetic resonance imaging/
16	(mr or mri or magnetic resonance).ti,ab.
17	14 or 15 or 16
18	thalamotomy/
19	(thalamus or thalamot*).ti,ab.
20	18 or 19
21	13 and 17
22	13 and 20
23	17 and 20
24	5 or 6 or 7 or 8 or 21 or 22 or 23
25	4 and 24
26	(conference or conference abstract or conference paper or "conference review" or editorial or letter o or "review").pt. or case report.ti,ab.
27	25 not 26
28	limit 25 to "reviews (maximizes specificity)"
29	27 or 28
30	limit 29 to (english language and yr="2009 -Current")

11 Evidence Selection

- Total number of publications reviewed: 41
- Total number of publications considered potentially relevant: 14
- Total number of publications selected for inclusion in this briefing: 6

References from the PWG supplied in the PPP		Paper selection decision and rationale if excluded
1	Chang JW, Park CK, Lipsman N, Schwartz ML, Ghanouni P, Henderson JM, Gwinn R, Witt J, Tierney TS, Cosgrove GR, Shah BB, Abe K, Taira T, Lozano AM, Eisenberg HM, Fishman P, Elias WJ. A Prospective Trial of Magnetic Resonance-Guided Focused Ultrasound Thalamotomy for Essential Tremor: Results at the 2-Year Follow Up. Annals of Neurology 2018; 83:107-114.	Included
2	Ravikumar VK, Parker JJ, Hornbeck TS, Santini VE, Pauly KB, Wintermark M, Ghanouni P, Stein SC, Halpber CH. Cost-Effectiveness of Focused Ultrasound, Radiosurgery, and DBS for Essential Tremor. Movement Disorders 2017; 32(8):1165-1173.	Included
3	Elias WJ, Lipsman N, Ondo WG. A Randomized Trial of Focused Ultrasound Thalamotomy for Essential Tremor. New England Journal of Medicine 2016; 375:730-739.	Included

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Elias WJ, Lipsman N, Ondo WG, Ghanouni P, Kim YG, Lee W, Schwartz M, Hynynen K, Lozano AM, Shah BB, Huss D, Dallapiazza RF, Gwinn R, Witt J, Ro S, Eisenberg HM, Fishman PS, Gandhi D, Halpern CH, Chuang R, Pauly KB, Tierney TS, Hayes MT, Cosgrove GR, Yamaguchi T, Abe K, Taira T, Chang JW. 2016. A randomized trial of focused ultrasound thalamotomy for essential tremor. *NEJM* 375: 730-739.

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Louis ED, Ferreira JJ. 2010. How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. *Movement Disorders* 25: 534-541.

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National Institute for Health and Care Excellence 2018. Unilateral MRI-guided focused ultrasound thalamotomy for treatment-resistant essential tremor: Interventional Procedures Guidance 617. www.nice.org.uk/guidance/ipg617 (accessed 24 May 2019)

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