NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of unilateral MRI-guided focused ultrasound thalamotomy for treatment-resistant essential tremor

Essential tremor has no known cause but may get worse with time and be resistant to treatment. This procedure uses a special head frame that allows ultrasound to be applied to a specific area on 1 side of the brain (thalamus) with MRI guidance. The aim is to reduce the tremors.

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Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in March 2017 and updated in March 2018.

Procedure name

- Unilateral MRI-guided focused ultrasound (MRgFUS) thalamotomy for treatment-resistant essential tremor

Specialist societies

- British Society of Interventional Radiology
- British Society of Neurological Surgeons
- Association of British Neurologists
- Royal College of Surgeons.

Description of the procedure

Indications and current treatment

Essential tremor is the most common cause of disabling tremor and is distinct from Parkinson's disease. It typically affects the arms and hands, although it may also involve the head, jaw, tongue and legs. The cause is not known but many patients have a family history of the condition. At first, the tremor may not be present all the time. However, it gradually worsens. Purposeful movement, stress, tiredness, hunger, heightened emotions or extremes in temperature make it worse.

Treatment for essential tremor includes medications such as beta blockers (for example, propranolol), anti-epileptics (for example, primidone) and sedatives (for example, clonazepam). Rarely, injections of botulinum toxin may be used.

Surgery may be considered in people whose condition has not responded adequately to best medical therapy. Surgical treatments include deep brain stimulation (DBS) and radiofrequency thalamotomy.

What the procedure involves

This procedure is carried out with the patient lying supine inside an 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. However, they may be offered light sedation. 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 3 hours and symptom relief should be immediate.

The potential benefits of unilateral MRI-guided focused ultrasound thalamotomy are that: it is less invasive than the other existing procedures; results in a faster recovery time; and allows for testing of the effects of sub-lethal doses before ablation. However, it is only done on 1 side.

Outcome measures

Clinical Rating Scale for Tremor (CRST)

The CRST is used to assess the severity of tremor. Scores range from 0 to 4 per component assessed and higher scores indicate more severe tremor.

Efficacy summary

Procedure success

In a comparative study of 59 patients who had MRgFUS thalamotomy (n=23), radiofrequency thalamotomy (n=17) or DBS (n=19), there was no statistically significant difference in procedure success (defined as absence of or greater than 90% abolition of symptoms) between groups at 1 month and 12 months (p=0.54 and 0.62 respectively). At 12 months, the procedure success rate was 78% (18/23) in the MRgFUS group, 71% (12/17) in the radiofrequency group and 84% in the DBS group.[3]

Tremor

In a randomised controlled trial (RCT) of 76 patients with essential tremor comparing MRgFUS thalamotomy (n=56) with sham (n=20), the mean±standard deviation (SD) CRST scores for hand tremor (scale ranges from 0 to 32, with higher scores indicating more severe tremor) statistically significantly improved from 18.1±4.8 at baseline to 9.6±5.1 at 3-month follow-up (47% improvement from baseline, p value not reported) and to 10.9±4.5 at 1 year (40% improvement from baseline; 95% confidence interval [CI] 6.1 to 8.3, p<0.001) in the treatment group. In the sham group, there was no statistically significant change in the CRST score for hand tremor from baseline (16.0±4.4) to 3-month follow-up (15.8±4.9; 0.1% change). The difference in the mean change was statistically significant between the 2 groups at 3 months (8.3 point difference; 95% CI 5.9 to 10.7; p<0.001). In the same study, the mean change in CRST score for total tremor (the maximum overall score for the most severe tremor is 152 points without supine assessments) from baseline was also statistically significantly different between the groups at 3 months (41% compared with 2%, p<0.001).[1]

In a 2-year follow-up cohort from the RCT of 76 patients, the CRST scores part A and B for hand tremor statistically significantly improved from 19.8±4.9 (n=76) at baseline to 8.8±5.0 (n=67) after 2 years (p<0.001).[2]

In a comparative study of 85 patients (15 patients who had unilateral focused ultrasound compared with 57 patients who had bilateral DBS compared with 13 patients who had unilateral DBS), there was a statistically significant improvement from baseline after the procedure in the CRST total score (maximum total score of 160) in all the groups from 54.9 to 17.7 in the focused ultrasound group, from 64.4 to 13.2 in the bilateral DBS group and from 59.5 to 15.8 in the unilateral DBS group (p<0.05). There was a statistically significantly smaller improvement in the unilateral focused ultrasound group than in the bilateral DBS group (p<0.05).[4]

In a case series of 30 patients, there was a statistically significant improvement in the CRST score from 40.7±11.6 at baseline to 8.2±5.0 at 6 months in the patients with essential tremor (n=18,

p<0.001). In the patients with essential tremor who developed Parkinson's disease many years later (n=3), the unified Parkinson's disease rating scale (UPDRS) score improved from 34.7±7.1 to 17.1±7.1 at 6 months (no statistical analysis conducted). [5]

In a case series of 21 patients with essential tremor who had MR-guided focused ultrasound cerebellothalamic tractotomy, the mean±SD essential (E) TRS score (scale ranges from 0 to 144, with higher scores indicating more severe tremor) had improved from 57.6±13.2 to 25.8±17.6 (55% reduction) 1 year after the procedure (p value not reported). In the same study, the hand function 16 score (higher scores indicate more severe tremor) had statistically significantly improved at 3 months and 1 year after the procedure by 74% and 78% respectively (p<0.001). Global tremor relief (mean patient estimation) was 92% at 2 days and 77% at 1 year.[6]

In a case series of 15 patients with essential tremor who had MRgFUS thalamotomy, the mean±SD CRST scores had statistically significantly improved from 20.4±5.2 to 5.2±4.8 at 1 year for contralateral hand tremor (75% improvement, p=0.01) and from 54.9±14.4 to 24.3±14.8 for total tremor (56% improvement, p=0.001); the CRST score did not change for ipsilateral hand tremor (p=0.90).[7]

In a case series of 11 patients (results from 8 patients analysed) with essential tremor who had MRgFUS thalamotomy, the mean scores of parts A, B and C of the CRST all statistically significantly improved at 6-month follow-up (part A – from 5.1 to 1.4; part B – from 13.0 to 2.6; part C – from 14.5 to 2; p=0.011).[8]

In a case series of 4 patients with essential tremor who had MRgFUS thalamotomy, the mean reduction in CRST score of the treated hand was 81% at 3 months. In the same study, the mean reduction in total impairment score on motor tasks (part B of the CRST) was 40% at 3 months (p value not reported).[9]

In a case series of 6 patients, both the overall tremor severity and the unilateral hand score on the treated side statistically significantly improved; the overall tremor severity CRST score improved from 43.8±9.8 at baseline to 19.8±6.8 at 6 months (95% CI 18.1 to 29.9; p<0.001) and the unilateral CRST hand score on the treated side improved from 14.3±4.9 to 2.5±2.6 (95% CI 8.4 to 15.2; p<0.001).[10]

In a systematic review and meta-analysis of 412 patients with essential tremor (efficacy cohorts), the mean tremor reduction (measured using Hedge's g [95% CI]) was similar between groups (a negative effect size indicates improvement of tremor): MRIgFUS targeting the cerebellothalamic tract (n=27), -2.35 (-2.51 to 2.19); MRIgFUS targeting the ventral intermediate nucleus (n=79), -2.08 (-2.77 to 1.39); radiofrequency targeting the ventral intermediate nucleus (n=25), -2.42 (-5.26 to 0.43) and Gammaknife (n=254), -2.13 (-3.78 to -0.48).[11]

Tremor recurrence

In the case series of 30 patients, the tremor recurred in 11% (2/18) of patients with essential tremor and in 67% (2/3) of patients with essential tremor who developed Parkinson's disease later.[5]

Functional activities of daily living

In the RCT of 76 patients with essential tremor, the mean improvement in the total disability score in part C of the CRST was statistically significantly greater in the MRgFUS thalamotomy group than in the sham group at 3 months (62% compared with 3%, p<0.001).[1]

In the 2-year follow-up cohort from the RCT of 76 patients, the disability score (8 items from part C of the CRST) statistically significantly improved from 16.4±4.5 (n=76) at baseline to 6.5±5.0 (n=67) after 2 years (p<0.001).[2]

In the comparative study of 85 patients, there was a statistically significant improvement from baseline after the procedure in the disability score (CRST part C, maximum score of 32) in all the groups from 18.2 to 2.8 in the focused ultrasound group, from 19.9 to 2.3 in the bilateral DBS group and from 18.9 to 3.2 in the unilateral DBS group (p<0.05).[4]

In the case series of 15 patients, the mean CRST disability score (scale ranges from 0 to 32, with higher scores indicating more disability) statistically significantly improved from 18.2±4.1 at baseline to 2.8±3.4 at 1-year follow-up (p=0.001). In the same study, the mean physical performance test score (ranging from 0 to 32, with higher scores indicating better performance) also statistically significantly improved from 22.9±3.0 to 27.1±2.7 at 1-year follow-up (p=0.001).[7]

In the case series of 4 patients, the mean reduction in perceived functional disability related to tremor (part C of the CRST) was 51% 3 months after the procedure (p value not reported).[9]

Quality of life

In the RCT of 76 patients, the mean improvement in the self-reported Quality of Life in Essential Tremor questionnaire (QUEST) score (scale ranges from 0 to 100, with higher scores indicating greater perceived disability) was statistically significantly greater in the treatment group (46% improvement from 42.6±18.3 to 23.1±16.9) than in the sham group (3% improvement) at 3 months (p<0.001).[1]

In the comparative study of 85 patients, there was no statistically significant difference in QUEST score improvement after the procedure in any of the domains of the QUEST questionnaire between the unilateral focused ultrasound group and the bilateral DBS group. The QUEST scores statistically significantly improved in both groups after the procedure, by 68.0% in the unilateral focused ultrasound group and by 72.0% in the bilateral DBS group (p<0.05 for the improvement from baseline).[4]

In the case series of 30 patients, there was a statistically significant improvement in the QUEST score from 44.8±12.9 at baseline to 12.3±7.2 at 6 months in the patients with essential tremor (n=18, p<0.001).[5]

In the case series of 15 patients, the QUEST score statistically significantly improved from 37% to 12% at 1 year (p=0.001).[7]

In the case series of 6 patients, the QUEST score statistically significantly improved from 50.5±19.4 at baseline to 24.8±11.4 at 6 months (95% CI 3.5 to 47.3, p=0.046).[10]

Safety summary

Complication rate

In a comparative study of 59 patients who had MRgFUS thalamotomy (n=23), radiofrequency thalamotomy (n=17) or DBS (n=19), there was a statistically significant difference in the complication rates between treatments at 1 month (13% [3/23], 59% [10/17] and 5% [1/19] respectively) and at 12 months (4% [1/23], 12% [2/17] and 21% [4/19] respectively; p<0.01). When modifiable complications (defined as complications that disappeared with parameter modulation) from DBS were excluded, there was no statistically significant difference in the complication rate between the DBS and MRgFUS groups.[3]

In a systematic review and meta-analysis of 273 patients with essential tremor (cohorts used to measure safety), there was no statistically significant difference between groups in the mean rates of persistent side effects (swallowing difficulties, sensory changes only; p=0.21); MRIgFUS targeting the cerebellothalamic tract (n=6): 0%±0%; MRIgFUS targeting the ventral intermediate nucleus (n=82): 19%±16%; radiofrequency targeting the ventral intermediate nucleus (n=32): 9%±9%; and Gammaknife (n=153): 2%±3%.[11]

Safety events reported during the procedure

In a RCT of 76 patients with essential tremor comparing MRgFUS thalamotomy with a sham procedure, intraprocedural sensations and events were brief and resolved by the end of the procedure. Five thalamotomy procedures were interrupted or suspended because of pain, nausea, vertigo, or vomiting.[1]

In a case series of 30 patients, the adverse events related to sonication reported were as follows: vertigo in 47% (14/30) of patients, headache in 37% (11/30), dizziness in 13% (4/30), nausea in 10% (3/30), burning scalp sensation in 10% (3/30), vomiting in 7% (2/20) and lip paraesthesia in 7% (2/30). They all resolved within seconds to minutes.[5]

In a case series of 6 patients, vestibular symptoms were reported during the procedure in 67% (4/6) of patients; they exclusively occurred during the final sonications that delivered the highest acoustic power per patient.[10]

Head discomfort or pain

Head discomfort ('heat' or 'pressure') was reported in 30% (17/56) of patients in the MRgFUS thalamotomy group and in none of the patients in the sham group (n=20) in the RCT of 76 patients within 1 year of the procedure (p value not reported).[1]

Headache was reported in 60% (9/15) of patients who had unilateral focused ultrasound during the procedure and in none of the patients who had bilateral or unilateral DBS in a comparative study of 85 patients.[4]

Head pain that occurred only during sonication was reported in 60% (9/15) of patients in the case series of 15 patients.[7]

Vestibular symptoms

Dizziness was reported in 21% (12/56) of patients in the treatment group and in none of the patients in the sham group in the RCT of 76 patients within 1 year of the procedure. In the same study, within 1 year of the procedure, nausea was reported in 20% (11/56) of patients in the treatment group and in 10% (2/20) of patients in the sham group, and vomiting was reported in 4% (2/56) of patients in the treatment group compared to none of the patients in the sham group (p values not reported).[1]

Dizziness that continued 2 years after the procedure was reported in 1 patient in a 2-year follow-up cohort from the RCT of 76 patients.[2]

Light headedness or dizziness was reported in 73% (11/15) of patients who had unilateral focused ultrasound during the procedure and in none of the patients who had bilateral or unilateral DBS in a comparative study of 85 patients. Nausea or vomiting was reported in 53% (8/15) of patients who had unilateral focused ultrasound during the procedure and in none of the patients in the other 2 groups.[4]

Unsteady feeling was reported in 13% (4/30) of patients in the case series of 30 patients. This resolved within 1 week to 4 weeks.[5]

Tilting, falling or a spinning sensation that only occurred during sonication was reported in 33% (5/15) of patients in the case series of 15 patients. In the same study, light headedness was reported in 40% (6/15), nausea in 33% (5/15) and vomiting in 20% (3/15) during sonication.[7]

Vestibular symptoms such as dizziness, nausea and vomiting during sonication were reported in 45% (5/11) of patients in a case series of 11 patients.[8]

Scalp tingling

Scalp tingling was reported in 7% (4/56) of patients in the treatment group and in 5% (1/20) of patients in the sham group in the RCT of 76 patients within 1 year of the procedure (p value not reported).[1]

Back pain

Back pain was reported in 9% (5/56) of patients in the treatment group and in 5% (1/20) of patients in the sham group in the RCT of 76 patients within 1 year of the procedure (p value not reported).[1]

Anxiety

Anxiety was reported in 5% (3/56) of patients in the treatment group and in 10% (2/20) of patients in the sham group in the RCT of 76 patients within 1 year of the procedure (p value not reported). [1]

Flushing or a warm sensation

Flushed warmth was reported in 27% (4/15) of patients who had unilateral focused ultrasound during the procedure and in none of the patients who had bilateral or unilateral DBS in the comparative study of 85 patients.[4]

Flushing or a warm sensation that only occurred during sonication was reported in 27% (4/15) of patients in the case series of 15 patients. [7]

Fainting

Fainting that occurred only during sonication was reported in 1 patient in the case series of 15 patients. [7]

Paresis

Mild facial paresis was reported in 4% (1/23) of patients in the MRgFUS group, in 18% (3/17) of patients in the radiofrequency group and in 5% (1/19) of patients in the DBS group in the comparative study of 59 patients.[3]

Paraesthesia or numbness

Paraesthesia or numbness was reported in 38% (21/56) of patients in the treatment group and in 5% (1/20) of patients in the sham group in the RCT of 76 patients within 1 year of the procedure. In the treatment group, they concerned the face and hand regions in 11% (6/56) of patients, the face, lips and tongue in 14% (8/56), the hand and fingers in 11% (6/56), and the leg in 2% (1/56) (p values not reported).[1]

Paraesthesia that continued 12 months after the procedure was reported in 10 patients in the 2-year follow-up cohort from the RCT of 76 patients. It resolved by the 2-year follow-up. [2]

Transient paraesthesia was reported in 93% (14/15) of patients who had unilateral focused ultrasound, in 4% (2/57) of patients who had bilateral DBS and in 8% (1/13) of patients who had unilateral DBS in the comparative study of 85 patients. Paraesthesia was reported at the 12-month follow-up in 20% (3/15), 2% (1/57) and 15% (2/13) of patients respectively.[4]

Paraesthesia of the lip or tongue was reported in 73% (11/15) of patients in the case series of 15 patients; it was transient in 60% (9/15) of patients and still present at 1-year follow-up in 13% (2/15) of patients. In the same study, paraesthesia of the finger was reported in 40% (6/15) of patients; it was transient in 33% (5/15) and still present at 1-year follow-up in 7% (1/15). [7]

Paraesthesia that developed during sonication was reported in 2 patients in a case series of 4 patients. It was presumably related to the spread of the lesion to afferent sensory axons or the sensory relay nucleus of the thalamus. In 1 patient it resolved after the completion of each sonication. However, the other patient had paraesthesias in the tips of the thumb and index finger that persisted at the 3-month follow-up and the procedure was stopped.[9]

Dysesthesia

Dysesthesia of the index finger was reported in 2 patients in the case series of 15 patients; it was transient in 1 patient and still present at 1-year follow-up in the other patient.[7]

Taste disturbance

Taste disturbance was reported in 5% (3/56) of patients in the treatment group and in none of the patients in the sham group in the RCT of 76 patients within 1 year of the procedure (p value not reported). [1]

Taste disturbance that continued 2 years after the procedure was reported in 1 patient in the 2-year follow-up cohort from the RCT of 76 patients.[2]

Loss of taste was reported in 1 patient out of 23 in the MRgFUS group, in 1 patient out of 17 in the radiofrequency group and in none of the patients in the DBS group in the comparative study of 59 patients.[3]

Taste disturbance was reported in 13% (4/30) of patients in the case series of 30 patients. This resolved within 1 month to 3 months.[5]

Gait disturbance

Objective or subjective gait disturbance was reported in 36% (20/56) of patients in the treatment group and in 5% (1/20) of patients in the sham group in the RCT of 76 patients within 1 year of the procedure (p value not reported). Ataxia noted objectively on examination was reported in 20% (11/56) of patients, and unsteadiness or unbalance reported subjectively by the examiner or by the patient were reported in 16% (9/56) of patients. Five patients with gait disturbances were prescribed physical therapy, and 1 patient with persistent ataxia needed a walker to walk.[1]

Gait disturbance that continued 2 years after the procedure was reported in 10 patients in the 2-year follow-up cohort from the RCT of 76 patients. In the same study, dysmetria and dysergia that continued 12 months after the procedure were reported in 1 patient each. Dysergia resolved by the 2-year follow-up.[2]

Balance problem was reported in 1 patient in the MRgFUS group, in none of the patients in the radiofrequency group and in 16% (3/19) of patients in the DBS group in the comparative study of 59 patients.[3]

Transient gait instability was reported in 33% (5/15) of patients who had unilateral focused ultrasound, in 18% (10/57) of patients who had bilateral DBS and in 85% (11/13) of patients who had unilateral DBS in the comparative study of 85 patients. There was no report of gait instability at the 12-month follow-up in any of the groups.[4]

Gait ataxia was reported in 17% (5/30) of patients (including 3 patients with essential tremor and 1 patient with essential tremor who developed Parkinson's disease later) in the case series of 30 patients. This resolved within 1 month to 3 months.[5]

Worsening of pre-existing gait instability with maximal worsening of 1 point over 4 (mean 0.7/4±0.3) was reported in 24% (5/21) of patients in a case series of 21 patients who had MR-guided focused ultrasound for essential tremor. At the last follow-up (3 months to 1 year), only 1 patient did not fully recover to his original walking ability, which was 0.5 points worse than preoperatively.[6]

A transient 'unsteady' feeling was reported in 33% (5/15) of patients in the case series of 15 patients. In the same study, ataxia lasting less than a month was reported in 27% (4/15) of patients.[7]

Transient mild balance problems due to swelling next to the medial lemniscus was reported in 1 patient in the case series of 11 patients. This was treated with oral corticosteroid therapy for 1 month.[8]

Gait instability and objective tendency to veer to the treated side were reported in 1 patient each in the case series of 6 patients; they resolved within 3 months.[10]

Complications of the hand

Hand ataxia was reported in 10% (3/30) of patients (2 patients with essential tremor and 1 patient with essential tremor who developed Parkinson's disease later) in the case series of 30 patients. This resolved within 1 week to 4 weeks.[5]

Subjective transient clumsiness of the treated hand was reported in 1 patient in the case series of 6 patients; it resolved within 3 months.[10]

Limb dysmetria

Limb dysmetria was reported in 12% (7/56) of patients in the treatment group and in none of the patients in the sham group in the RCT of 76 patients within 1 year of the procedure (p value not reported).[1]

Dysmetria, which lasted less than 1 month, was reported in 1 patient in the case series of 15 patients.[7]

Weakness

Contralateral weakness was reported in 4% (2/56) of patients in the treatment group and in none of the patients in the sham group in the RCT of 76 patients within 1 year of the procedure (p value not reported).[1]

Muscle weakness that continued 2 years after the procedure was reported in 1 patient in the 2-year follow-up cohort from the RCT of 76 patients.[2]

Transient weakness was reported in 7% (1/15) of patients who had unilateral focused ultrasound, in 7% (4/57) of patients who had bilateral DBS and in 8% (1/13) of patients who had unilateral DBS in the comparative study of 85 patients. Weakness was reported at the 12-month follow-up in none of the patients who had unilateral focused ultrasound or unilateral DBS and in 2% (1/57) of patients who had bilateral DBS.[4]

Weak grip, which lasted for 5 days after the procedure, was reported in 1 patient in the case series of 15 patients.[7]

Dysarthria

Dysarthria was reported in 1 patient out of 56 in the treatment group and in none of the patients in the sham group in the RCT of 76 patients within 1 year of the procedure (p value not reported).[1]

Transient dysarthria was reported in 7% (1/15) of patients who had unilateral focused ultrasound, in 18% (10/57) of patients who had bilateral DBS and in 8% (1/13) of patients who had unilateral DBS in the comparative study of 85 patients. Dysarthria was reported at the 12-month follow-up in none of the patients who had unilateral focused ultrasound or unilateral DBS and in 11% (6/57) of patients who had bilateral DBS.[4]

Slurred speech, which lasted for 1 day after the procedure was reported in 1 patient in the case series of 15 patients.[7]

Dysphagia

Dysphagia was reported in 1 patient out of 56 in the treatment group and in none of the patients in the sham group in the RCT of 76 patients within 1 year of the procedure (p value not reported).[1]

Headache

Headache lasting more than 1 day was reported in 14% (8/56) of patients in the treatment group and in 20% (4/20) of patients in the sham group in the RCT of 76 patients within 1 year of the procedure (p value not reported).[1]

Fatigue

Fatigue was reported in 5% (3/56) of patients in the treatment group and in 1 patient in the sham group (n=20) in the RCT of 76 patients within 1 year of the procedure (p value not reported).[1]

Asthenia was reported in 13% (4/30) of patients in the case series of 30 patients. This resolved within 1 week to 4 weeks.[5]

Disequilibrium sensation

Disequilibrium sensation was reported in 9% (5/56) of patients in the treatment group and in none of the patients in the sham group (n=20) in the RCT of 76 patients within 1 year of the procedure (p value not reported).[1]

Tinnitus

Tinnitus was reported in 5% (3/56) of patients in the treatment group and in none of the patients in the sham group (n=20) in the RCT of 76 patients within 1 month of the procedure (p value not reported).[1]

Transient ischemic attack

A transient ischemic attack was reported in 1 patient in the unblinded cohort of patients having focused ultrasound thalamotomy 6 weeks after the procedure in the RCT of 76 patients. It resolved within 3 days.[1]

Deep vein thrombosis

Deep vein thrombosis in the lower limb was reported in 1 patient around 1 week after the procedure in the case series of 4 patients. It needed anticoagulation treatment for 3 months. This event might have been related to the length of the procedure.[9]

Safety events attributable to the placement of the stereotactic frame

Pin-site pain, oedema, or bruising attributable to the placement of the stereotactic frame were reported in 30% (17/56) of patients in the treatment group and in 35% (7/20) of patients in the sham group in the RCT of 76 patients within 1 month of the procedure (p value not reported).[1]

MRI burn at the frame pin site was reported in 13% (2/15) of patients who had unilateral focused ultrasound and in none of the patients who had bilateral or unilateral DBS in the comparative study of 85 patients.[4]

Scalp numbness was reported in 17% (5/30) of patients in the case series of 30 patients. This resolved within 1 week to 4 weeks. In the same study, haematoma near the eye was reported in 10% (3/30) of patients; it resolved within1 week to 2 weeks.[5]

Headache that lasted more than 1 day after the procedure and scalp numbness in occipital region were both reported in 27% (4/15) of patients in the case series of 15 patients. In the same study, pin-site laceration and periorbital oedema were both reported in 1 patient each and scalp burn from pin-site heating was reported in 13% (2/15) of patients.[7]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, the specialist advisers listed the following anecdotal adverse event: sensation of spinning during the procedure. They considered that the following were theoretical adverse events: intracranial haemorrhage, stroke, increased intracranial pressure, the effect wearing off over a longer time period and permanent unintended neurological complications.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to unilateral MRgFUS thalamotomy for treatment-resistant essential tremor. The following databases were searched, covering the period from their start to 4 March 2018: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with treatment-resistant essential tremor.
Intervention/test	Unilateral MRI-guided focused ultrasound thalamotomy.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 298 patients from 1 systematic review and meta-analysis[11], 1 RCT (2 publications providing 1- and 2-year follow-up data)[1, 2], 2 non-randomised comparative studies[3, 4] and 6 case series[5-10].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in the appendix.

Table 2 Summary of key efficacy and safety findings on unilateral MRI-guided focused ultrasound thalamotomy for treatment-resistant essential tremor

Study 1 Elias W J (2016)

Details

Study type	**Prospective double-blind RCT**
Country	Worldwide (8 centres)
Recruitment period	2013-14
Study population and number	n=**76 (56 FUS thalamotomy versus 20 sham)** patients with moderate-to-severe essential tremor
Age and sex	• FUS thalamotomy: mean 71 years; 66% (37/56) male • Sham: mean 71 years; 75% (15/20) male
Patient selection criteria	Inclusion criteria: postural or intention tremor of the hand that was moderate to severe (score of ≥2 on the CRST) and disabling (score of ≥2 on any of the 8 items in the disability subsection of the CRST). Tremor that was refractory to at least 2 trials of medical therapy, including at least 1 first-line agent. For patients having concurrent medical therapy, medication doses had to be stable for 30 days before randomisation. Exclusion criteria: neurodegenerative condition, unstable cardiac disease, coagulopathy, risk factors for deep vein thrombosis, severe depression, cognitive impairment or previous brain procedure. A skull density ratio of less than 0.45 from the screening computed tomographic scan.
Technique	• FUS thalamotomy: after stereotactic targeting with the use of MRI, acoustic energy was sequentially titrated to temperatures sufficient for tissue ablation (approximately 55 to 60°C). Each brief sonication was monitored with magnetic resonance thermometry. • Sham procedure: an identical procedure was done with a randomised number of sonications for which the acoustic power was disengaged so that no acoustic energy was delivered to the brain.
Follow-up	**1 year**
Conflict of interest/source of funding	The study was partially funded by InSightec.

Analysis

Follow-up issues:

- 81 patients were enrolled and randomly assigned to a study group. Five of these patients were excluded before having the assigned procedure because they met exclusionary criteria. As predefined in the protocol and statistical analysis plan, only the 76 patients in whom the study procedure was attempted or completed were included in the modified intention-to-treat analysis.
- 97% (74/76) of patients completed study visits throughout the 3-month primary assessment period, and 91% of the thalamotomy group were assessed through 12 months.

Study design issues:

- Given a sample of at least 60 patients, the study had almost 100% power to show the primary efficacy of thalamotomy, assuming average improvements of 78% and 4% in the thalamotomy and sham-procedure groups respectively (standard deviation, 25%).
- A total of 21 participants (19 assigned to the sham-procedure group who crossed over to thalamotomy and 2 assigned to thalamotomy in whom the procedure was incomplete) were treated after the 3-month blinded assessment period.
- The CRST and the Quality of Life in Essential Tremor Questionnaire were administered at baseline and at 1, 3, 6, and 12 months.
- Tremor assessments were videotaped and rated by an independent group of neurologists who were unaware of the treatment assignments.
- The primary outcome was the between-group difference in the change from baseline to 3 months in hand tremor, rated on a 32-point scale (with higher scores indicating more severe tremor). The tremor score was derived from the CRST, Part A (3 items: resting, postural, and action or intention components of hand tremor), and the CRST, Part B (5 tasks involving handwriting, drawing, and pouring), in the hand contralateral to the thalamotomy.
- After 3 months, patients in the sham-procedure group could cross over to active treatment (the open-label extension cohort).
- The study participants and the neurologist at each site were unaware of the treatment assignments throughout the first 3 months, and the primary assessors of the videotaped tremor evaluations were not involved in the study treatments and were unaware of the treatment assignments and the side that was treated. Since the patients' heads were not covered, the assessors could see whether the videotapes showed preoperative or postoperative tremor evaluations; however, they could not determine whether the videotapes were taken 1, 3, 6, or 12 months after treatment.

Study population issues: The 76 patients had a mean (±SD) disease duration of 16.8±12.3 years.

Other issues:

- Procedures were all done unilaterally.
- Transcranial delivery of FUS was difficult to achieve in 5 patients, probably because of the frequency and other properties of the acoustic wave, as well as individual cranial characteristics.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **76 (56 FUS thalamotomy versus 20 sham)**

Hand tremor (CRST score, mean score±SD [% improvement from baseline], scale ranging from 0 to 32, with higher scores indicating more severe tremor)

	FUS thalamotomy (n=56)	Sham (n=20)	Unblinded cohort who had FUS thalamotomy (n=21)
Baseline	18.1±4.8	16.0±4.4	16.5±4.2
3 months	9.6±5.1 (47% improvement)	15.8±4.9 * (0.1% change)	7.4±3.9 (55% improvement, p<0.001)
1 year	10.9±4.5 (40% improvement) Change from baseline: 7.2 points; 95% CI 6.1 to 8.3 (p<0.001)	-	8.0±3.9 (52% improvement, p<0.001)

*Between-group difference in the mean change at 3 months: 8.3 points (95% CI 5.9 to 10.7; p<0.001).

The tremor score for the hand ipsilateral to the thalamotomy showed no statistically significant change (from 11.8±5.5 at baseline to 11.6±5.5 at 3 months, p=0.50).

Total tremor (CRST score, mean score±SD, maximum overall score for the most severe tremor, 152 points without supine assessments)

	FUS thalamotomy	Sham	p value
Baseline	50.1±14.0	44.1±12.7	
3 months	29.6±13 (41% improvement)	43.1±13.1 (2% change)	<0.001 (between-group comparison of the change at 3 months)
1 year	32.4±14.5 (35% improvement)	-	

The improvement in total tremor scores in the unblinded cohort (n=21) was similar to the improvement in the patients who had thalamotomy during the blinded phase.

Functional activities of daily living (total disability score from Part C of the CRST)

	FUS thalamotomy (n=56)	Sham (n=20)
Baseline	16.5±4.6	16.0±4.3
3 months**	6.2±5.6 (62% reduction)	15.6±4.6 (3% reduction)
1 year	6.3±6.2	-

Safety

Adverse events	FUS thalamotomy (n=56)							Sham (n=20)
	Total	D1	D7	1Mo	3Mo	6Mo	12 Mo[a]	
Paraesthesia or numbness								
Any region	38% (21)	18	17	16	14	11	14% (8)	5% (1)
Both face and hand	11% (6)	5	5	5	5	5	9% (5)	
Face, lips, and tongue	14% (8)	7	6	6	6	4	4% (2)	
Hand and fingers	11% (6)	5	5	4	2	1	2% (1)	5% (1)
Leg	2% (1)	1	1	1	1	1		
Taste disturbance	5% (3)	3	2	2	2	2	4% (2)	
Gait disturbance†								
Any, objective or subjective	36% (20)	19	18	13	9	7	9% (5)	5% (1)
Ataxia, noted objectively on examination	20% (11)	11	10	6	2	2	4% (2)	
"Unsteady" or "unbalanced," reported subjectively by examiner or patient	16% (9)	8	8	7	7	5	5% (3)	5% (1)
Dysmetria, limb	12% (7)	7	7	5	5	4	4% (2)	
Weakness, contralateral	4% (2)	2	2	2	2	2	2% (1)	
Dysarthria	2% (1)	1	1	1	1	1		
Dysphagia	2% (1)	1	1	1	1	1		
Headache lasting >1 day	14% (8)	8	4	4	2	2		20% (4)
Fatigue	5% (3)	3	3	2	1			5% (1)
Disequilibrium sensation	9% (5)	5	5	5	3	2	2 (1)	
Tinnitus	5% (3)	3	3	1				
Intraprocedural sensations or events‡								
Head discomfort: "heat" or "pressure"	30% (17)							
Vertigo: "dizzy"	21% (12)							
Nausea	20% (11)							10% (2)

** Statistically significant between-group difference in the mean change at 3 months (p<0.001).

The mean disability scores at baseline were highest for drinking and writing.

At 12 months, the score for every activity had improved, with a reduction to a score of 0 (normal) or 1 (mild disability) for each item except writing (1.21±1.14).

Patient-reported quality of life (QUEST score)

	FUS thalamotomy (n=56)	**Sham (n=20)**
Baseline	42.6±18.3	42.8±19.5
3 months* **	23.1±16.9 (46% reduction)	41.4±19.4 (3% reduction)

***Statistically significant between-group difference in the mean change at 3 months (p<0.001).

Vomiting	4% (2)							
Scalp tingling	7% (4)							5% (1)
Back pain	9% (5)							5% (1)
Anxiety	5% (3)							10% (2)
Pin-site pain, oedema, or bruising attributable to placement of the stereotactic frame	30% (17)							35% (7)
No adverse events	11% (6)							40% (8)

[a]Adverse events reported at 12 months are still ongoing.

† Five patients with gait disturbances were prescribed physical therapy, and 1 patient with persistent ataxia needed a walker for ambulation.

‡ Intraprocedural sensations and events were brief and resolved by the end of the procedure. Five thalamotomy procedures were interrupted or suspended because of pain, nausea, vertigo, or vomiting.

A similar profile of side effects was observed in the unblinded cohort of patients having FUS thalamotomy. One patient had a **transient ischemic attack** 6 weeks after having thalamotomy. It resolved within 3 days.

Abbreviations used: CI, confidence interval; CRST, Clinical rating scale for tremor; D, day; FUS, focused ultrasound; MRI, magnetic resonance imaging; QUEST, quality of life in essential tremor; Mo, month; RCT, randomised controlled trial; SD, standard deviation.

Study 2 Chang J W (2017) - *2-year follow-up of the Elias (2016) study*

Details

Study type	**RCT**
Country	Worldwide (8 centres)
Recruitment period	2013-14
Study population and number	Original cohort: n=**76 (56 FUS thalamotomy versus 20 sham)** patients with moderate-to-severe essential tremor 2-year follow-up cohort: n=**67 FUS thalamotomy** patients with moderate-to-severe essential tremor
Age and sex	• FUS thalamotomy: mean 71 years; 66% (37/56) male • Sham: mean 71 years; 75% (15/20) male
Patient selection criteria	Inclusion criteria: postural or intention tremor of the hand, which was moderate to severe (defined by a score of ≥2 on the CRST; scores range from 0 to 4 per component assessed, with higher scores indicating more severe tremor) and disabling (defined by a score of ≥2 on any of the 8 items in the disability subsection of the CRST [scores range from 0 to 4 per item, with higher scores indicating greater disability]). A skull density ratio of 0.45±0.05 or more was needed based on the screening CT scan. Doses of medication for ET must have been stable for 30 days before enrolment, and maintained without adjustment thereafter during the study. Exclusion criteria: diagnosis of a current or past psychiatric illness, current substance abuse, other neurological disorders (such as idiopathic Parkinson's disease) that affect brain function, contraindications for MRI, and known intolerance or allergies to the MRI contrast agent.
Technique	• FUS thalamotomy: after stereotactic targeting with the use of MRI, acoustic energy was sequentially titrated to temperatures sufficient for tissue ablation (approximately 55 to 60°C). Each brief sonication was monitored with magnetic resonance thermometry. • Sham procedure: an identical procedure was done with a randomised number of sonications for which the acoustic power was disengaged so that no acoustic energy was delivered to the brain.
Follow-up	**2 years**
Conflict of interest/source of funding	The study was supported by InSightec, the Focused Ultrasound Foundation and the Binational Industrial Research and Development (BIRD) Foundation (Israel). The sponsorship was part of the regulatory review process under the United States FDA. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Analysis

Follow-up issues: During 2-year follow-up, 9 patients were either lost to follow-up, had alternative treatment, or voluntarily withdrew from the study. The reasons for stopping were: diagnosis of skin cancer (1), diagnosis of stage 4 pancreatic cancer (1), unspecified (3), treatment by DBS (3), and treatment failure due to hyperostosis frontalis interna – difficulties to raise temperature at target (1). However, all patients who were evaluated at each follow-up period (6, 12, and 24 months), including patients who ultimately dropped-out, were analysed.

Study design issues:

- Videotaped standardised tremor evaluations obtained at the different centres were assessed by an independent core group of neurologists (Tremor Research Group) for tremor severity and functional impairment using the CRST (at baseline and at 6 months, 12 months and 24 months after treatment).

- The 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 (3 items: resting, postural, and action or intention components of hand tremor), and the CRST, Part B (5 tasks involving handwriting, drawing, and pouring), in the hand contralateral to the thalamotomy. The functional status was determined with the rating for the disability subsection (Part C) of the CRST. The "Posture" and the "Action or intention" components of the CRST-A were also evaluated. Adverse effects were sought and ascertained by open-ended and directed questions and by neurological examination.

Study population issues: The mean (± SD) disease duration of the 76 patients was 16.8±12.3 years. Most patients were right-handed (83%) and Caucasian (75%), and most had a family history of tremor (72%). The mean total CRST score for tremor severity was 49.5 (highest possible score, 152).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **67**

Hand tremor (CRST score Part A and B)

	Baseline (n=76)	6 months (n=75)	12 months (n=70)	24 months (n=67)	*p*-value
Hand tremor score	19.8±4.9	8.6±4.5	8.9±4.8	8.8±5.0	<0.001

At 2 years, 2 patients had no hand tremor (score 0) and approximately 62% of patients showed tremor scores that improved by greater or equal to 50%.

Functional improvement (disability score derived by summating 8 items of Part C of the CRST)

	Baseline (n=76)	6 months (n=75)	12 months (n=70)	24 months (n=67)	*p*-value
Disability score	16.4±4.5	5.4±4.7	5.4±5.3	6.5±5.0	<0.001

Posture score (single item derived from Part A of the CRST)

	Baseline (n=76)	6 months (n=75)	12 months (n=70)	24 months (n=67)	*p*-value
Posture score	2.9±1.0	0.8±1.0	0.8±1.0	0.9±1.0	<0.001

Action score (single item derived from Part A of the CRST)

	Baseline (n=76)	6 months (n=75)	12 months (n=70)	24 months (n=67)	*p*-value
Action score	2.9±0.7	1.2±0.9	1.4±0.9	1.4±0.9	<0.001

Safety

Adverse events that occurred at treatment time and continued at 12 months

Adverse event	n patients
Paraesthesia	10
Gait disturbance	10
Taste disturbance	1
Dysergia	1
Dysmetria	1
Muscle weakness	1
Dizziness	1

All events were mild or moderate. None of these events worsened at 2-year follow-up, and 2 of these events resolved (dysergia and paraesthesia).
There were no new complications or adverse events which related to MRgFUS thalamotomy from 12 months to 2 years after MRgFUS.

Abbreviations used: CRST, Clinical rating scale for tremor; CT, computed tomography; DBS, deep brain stimulation; ET, essential tremor; MRgFUS, MRI-guided focused ultrasound.

Study 3 Kim M (2017)

Details

Study type	**Retrospective comparative study**
Country	Korea
Recruitment period	1995-2014
Study population and number	n=**59 (23 MRgFUS versus 17 RF versus 19 DBS)** patients with drug-resistant essential tremor
Age and sex	MRgFUS: Mean 65 years RF: Mean 65 years DBS: Mean 63 years 71% (42/59) male
Patient selection criteria	Inclusion criteria: minimum follow-up of 1 year and a record of outcome assessments. Exclusion criteria: subsequent surgery after the initial procedure and bilateral DBS.
Technique	MRgFUS: use of the Exablate 4000 device. Sonication was applied to achieve thermal ablation with a peak target temperature of 55 to 62ºC. RF thalamotomy: The lesioning probe was heated to 65ºC for 60 seconds. DBS: Patients were treated under topical anaesthesia during electrode implantation and under general anaesthesia during the implantation of the pulse generator.
Follow-up	**1 year**
Conflict of interest/source of funding	Not reported

Analysis
Follow-up issues: The presence, type and severity of the tremor, and the treatment-related complications were evaluated before surgery, and 1 and 12 months after surgery.
Study design issues:
- All procedures were done by the same surgical team.
- Unilateral RF thalamotomy procedures were only done until 2004.
- Although the Fahn-Tolosa-Marin scale was used in the patients who had MRgFUS and DBS, it was not recorded for the patients who had RF thalamotomy and therefore it was not used for procedural comparisons in this study.

Study population issues: The mean disease duration was 21 years for MRgFUS and RF, and 14 year for the DBS group.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 59 (23 MRgFUS versus 17 RF versus 19 DBS)

Procedure success (absence of or occasional [defined as greater than 90% abolition] symptoms)
<table>
<tr><th></th><th>MRgFUS (n=23)</th><th>RF (n=17)</th><th>DBS (n=19)</th></tr>
<tr><td>1 month</td><td>91% (21/23)</td><td>100% (17/17)</td><td>89% (17/19)</td></tr>
<tr><td>12 months</td><td>78% (18/23)</td><td>71% (12/17)</td><td>84% (16/19)</td></tr>
</table>
No statistically significant difference in procedure success was observed between the groups at 1 and 12 months (p=0.54 and 0.62 respectively).
</td><td>
Complications
<table>
<tr><th></th><th>MRgFUS (n=23)</th><th>RF (n=17)</th><th>DBS (n=19)</th></tr>
<tr><td>1 month</td><td>13% (3/23)</td><td>59% (10/17)</td><td>5% (1/19)</td></tr>
<tr><td>12 months</td><td>4% (1/23)</td><td>12% (2/17)</td><td>21% (4/19)</td></tr>
</table>
There was a statistically significant difference in the complication rates between treatments (p<0.01). When modifiable complications (defined as complications that disappeared with parameter modulation) from DBS were excluded (i.e. balance problems), there was no statistically significant difference in the complication rate between the DBS and MRgFUS groups.

<u>MRgFUS group</u>
• Mild facial paresis: 4% (1/23)
The patient recovered within a month without medication. At 12 months, the facial paresis remained in a milder form.
• Balance problems: 4% (1/23)
The cause was brain oedema and the patient had oral corticosteroid therapy for 1 month.
• Loss of taste: 4% (1/23)
It resolved within a week.

<u>RF thalamotomy (complications are counted multiple times)</u>
• Intracerebral haemorrhage near the lesion: 12% (2/17)
• Cognitive deterioration: 6% (1/17)
• Mild dysarthria: 29% (5/17)
• Impaired eye movement: 6% (1/17)
• Mild facial paresis: 18% (3/17)
• Hypaesthesia: 6% (1/17)
• Loss of taste: 6% (1/17)

<u>DBS</u>
• Mild facial paresis: 5% (1/19)
It resolved completely within the first month after surgery.
• Balance problems: 16% (3/19)
These were relieved with stimulation adjustment.
• Muscle twitching in the contralateral forearm: 5% (1/19)
</td></tr>
<tr><td colspan="2">Abbreviations used: DBS, deep brain stimulation; MRgFUS, MRI-guided focused ultrasound; RF, radiofrequency.</td></tr>
</table>

Study 4 Huss D S (2015)

Details

Study type	**Retrospective comparative study**
Country	USA
Recruitment period	2004-13
Study population and number	n=**85 (15 unilateral FUS versus 57 bilateral DBS versus 13 unilateral DBS)** patients with medication-refractory essential tremor
Age and sex	Unilateral FUS: Mean 67 years; 67% (10/15) male Bilateral DBS: Mean 64 years; 67% (38/57) male Unilateral DBS: Mean 72 years; 62% (8/13) male
Patient selection criteria	Patients with medication-refractory ET and with preoperative and postoperative evaluation using the CRST and QUEST.
Technique	FUS thalamotomy with the NeuroAblate 4000 (Insightec), bilateral thalamic DBS or unilateral thalamic DBS.
Follow-up	**Unilateral FUS: Mean 12 months** **Bilateral DBS: Mean 13 months** **Unilateral DBS: Mean 9 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues:

- Ninety-seven patients with ET were evaluated and had DBS or FUS at the by a single neurosurgeon at a single centre. Twelve patients, all of whom were had DBS, with missing information or incomplete evaluations were excluded from the analysis.

- All post-treatment assessments for DBS patients were conducted with the DBS turned on. For patients who had FUS thalamotomy, CRST was evaluated at 12 months after surgery, except for 1 patient who only had a 3-month follow-up. Quality of life questionnaires were administered at the same visit as CRST evaluation. For unilateral DBS procedures, too few patients had preoperative and postoperative QUEST scores, so these patients were excluded from the analysis of QUEST outcomes.

Study design issues: Tremor was rated for all patients before and after treatment, using the Clinical Rating Scale for Tremor and Quality of Life in Essential Tremor Questionnaire.

Study population issues:

- The mean age for bilateral DBS was significantly younger than the mean age for unilateral DBS.

- Patients having bilateral DBS treatment had more baseline tremor and worse quality of life scores.

Other issues: This study comes from the same group and institution as all the Elias' papers.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **85 (15 unilateral FUS versus 57 bilateral DBS versus 13 unilateral DBS)**

Tremor (CRST score reported as points followed by percent change from baseline in parentheses)

	Unilateral FUS		Bilateral DBS		Unilateral DBS	
	Baseline	Postoperative	Baseline	Postoperative	Baseline	Postoperative
CRST total score (N/160)	54.9	17.7 (55.7)[a,b]	64.4	13.2 (79.5)[a]	59.5	15.8 (62.8)[a,b]
Part A, observed tremor (N/92)	13.4	8.7 (35.1)[a,b]	22.1	3.8 (82.8)[a]	19.1	8.4 (56.0)[a,b]
Part B, tasks (N/36)	23.6	12.7 (46.2)[a,b]	22.4	7.1 (68.3)[a]	21.5	10.2 (52.6)[a,c]
Part C, disability (N/32)	18.2	2.8 (85.4)[a]	19.9	2.3 (88.4)[a]	18.9	3.2 (83.1)[a]
Axial (N/44)	2.7	2.3 (14.8)[b]	6.2	0.3 (95.2)[a]	3.5	0.2 (94.3)[a]
Treated hand, (R if bilat), (N/32)	20.4	5.7 (74.5)[a]	20.4	5.2 (74.5)[a]	18.5	5.6 (78.9)[a]
Untreated hand. (L if bilat) (N/28)	13.4	24.3 (–0.7)[b]	17.1	6.9 (68.5)[a]	20.4	21.8 (–4.6)[b]

[a]Denotes statistically significant difference from baseline (p<0.05).

[b]Denotes statistically significant difference from bilateral DBS (p<0.05).

[c]Denotes statistically significant difference from bilateral DBS (p<0.012).

Quality of life (Quest scores)

	Unilateral FUS		Bilateral DBS	
	Baseline (% score)	Postoperative (% improvement)	Baseline (% score)	Postoperative (% improvement)
QUEST summary index	37.5	68.0[a]	52.1	72.0[a]
Communication	13.3	37.6	34.1	46.9[a]
Work	19.7	51.8[a]	33.0	87.6[a]
Hobbies	52.8	67.4[a]	54.7	67.5[a]
Physical	66.1	75.2[a]	78.2	76.7[a]
Social	35.9	75.8[a]	60.9	72.9[a]

[a]Denotes statistically significant difference from baseline (p<0.05).

No statistically significant difference between groups in QUEST score improvement in any of the domains of the QUEST questionnaire.

Safety

Adverse events

	Unilateral FUS		Bilateral DBS		Unilateral DBS	
Adverse events	0-3 mo	12 mo	0-3 mo	12 mo	0-3 mo	12 mo
Neurological						
Paraesthesia	93% (14/15)	20% (3/15)	4% (2/57)	2% (1/57)	8% (1/13)	15% (2/13)
Dysarthria	7% (1/15)	0	18% (10/57)	11% (6/57)	8% (1/13)	0
Dysphagia	0	0	4% (2/57)	0	0	0
Gait instability	33% (5/15)	0	18% (10/57)	0	85% (11/13)	0
Weakness	7% (1/15)	0	7% (4/57)	2% (1/57)	8% (1/13)	0
Mental status change	0	0	5% (3/57)	5% (3/57)	8% (1/13)	0
Physical (brief intraprocedural symptoms)						
Headache	60% (9/15)	0	0	0	0	0
Lightheaded/ dizzy	73% (11/15)	0	0	0	0	0
Nausea/vomiting	53% (8/15)	0	0	0	0	0
Flushed warmth	27% (4/15)	0	0	0	0	0
Hardware related						
Infection	0	0	0	2% (1/57)	0	0
Lead erosion	0	0	2% (1/57)	4% (2/57)	0	0
MRI burn at frame pin site	13% (2/15)	0	0	0	0	0
Haemorrhage	0	0	4% (2/57)	0	0	0

Abbreviations used: CRST, Clinical rating scale for tremor; DBS, deep brain stimulation; ET, essential tremor; FUS, focused ultrasound; L, left; mo, month; QUEST, quality of life in essential tremor; R, right.

Study 5 Zaaroor M (2017)

Details

Study type	**Case series**
Country	Israel
Recruitment period	2013-16
Study population and number	n=**30** patients including **3 with ET-PD (**patients with essential tremor who developed Parkinson's disease later in life)**, 18 with ET** and 9 with PD
Age and sex	Mean 69 years; 77% (23/30) male
Patient selection criteria	All patients were offered either DBS or MRgFUS and preferred MRgFUS as their treatment of choice. Inclusion criteria: patients with severe refractory tremor. Exclusion criteria: contraindications for the procedure including, but not limited to, significant cognitive decline, current anticoagulant or anti-aggregant therapy, brain tumours, vascular malformations, significant unstable medical conditions, and contraindications for MRI, including claustrophobia.
Technique	VIM thalamotomy contralateral to the patient's hand preference.
Follow-up	**6–24 months (mean 11.5 months)**
Conflict of interest/source of funding	None

Analysis

Study design issues:

- For ET, a clinically significant tremor was defined as a score of more than 2 on the postural or action item on the Clinical Rating Scale for Tremor (CRST; range 0–4), as well as substantial disability in the performance of at least 2 daily activities from the disability subsection of the scale.
- For ET-PD, tremor was measured by the motor part of the Unified PD Rating Scale (UPDRS) in the ON stage. A score of more than 3 (range 0–4) on either item 20 or 21 of the UPDRS was defined as a severe disabling tremor. ET-PD was diagnosed in patients with long-standing ET who developed PD symptoms many years later.
- Quality of life in patients with ET was measured by the Quality of Life in Essential Tremor (QUEST) questionnaire and quality of life in patients with ET-PD was measured by the PDQ-39.
- Assessment after the procedure was usually done 1 day, 1 week, 1–3 months, 6 months, and 1 year after treatment and was repeated yearly.

Study population issues:

- All patients had medication-resistant tremor. Twenty-four patients were right-handed. Tremor was more prominent on the right side in 22 of the patients.
- The mean disease duration was 12 years (range 2–30 years).
- 1 patient with ET-PD had levodopa.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **30** patients including **3 with ET-PD, 18 with ET** and 9 with PD

Tremor

	Patients with ET (n=18) CRST score				Patients with ET-PD (n=3) UPDRS Motor score		
	Baseline	**After 1 month**	**After 6 months**		**Baseline**	**After 1 month**	**After 6 months**
Score (mean±SD)	40.7±11.6	9.3±7.1 *	8.2±5.0 *		34.7± 7.1	22.7±7.5 **	17.1±7.1 **

*** p<0.001 for the comparison to baseline.**

**** No statistical analysis conducted.**

Hand tremor was abolished immediately after the procedure in all 30 patients. In 3 patients, an accompanying leg tremor was also abolished and in 2 other patients an accompanying head tremor was abolished as well.

Tremor recurrence during the first 6 months after the procedure (mean 2.5 months)

Patients with ET: 11% (2/18)

Patients with ET-PD: 67% (2/3)

The tremor that recurred was significantly less disabling than before the procedure in all but 1 patient with ET-PD.

Quality of life

	Patients with ET (n=18) QUEST score				Patients with ET-PD (n=2) PDQ-39 Score		
	Baseline	**After 1 month**	**After 6 months**		**Baseline**	**After 1 month**	**After 6 months**
Score (mean±SD)	44.8±12.9	13.1±13.2 [a]	12.3±7.2 [a]		24	7	14
					25	6	1

[a] **p<0.001 for the comparison to baseline.**

The improvement in quality of life was sustained in 94% of the patients with ET and in 66% of the patients with ET-PD.

Clinical assessment by the examiner and patients changed from severe disability to no functional disability immediately after the procedure in all patients. Twenty-nine of 30 patients reported subjective satisfaction from the procedure during follow-up.

Safety

Adverse Event	No. of Patients	Time to Resolution
Related to sonication		
Vertigo	47% (14/30)	Seconds
Headache	37% (11/30)	Seconds to minutes
Dizziness	13% (4/30)	Seconds to minutes
Nausea	10% (3/30)	Minutes
Burning scalp sensation	10% (3/30)	Seconds
Vomiting	7% (2/30)	Minutes
Lip paraesthesia	7% (2/30)	Seconds
Related to thalamotomy		
Gait ataxia	17% (5/30) (3 ET, 1 PD, and 1 ET-PD)	1–3 months
Unsteady feeling	13% (4/30)	1–4 weeks
Taste disturbance	13% (4/30)	1–3 months
Asthenia	13% (4/30)	1–4 weeks
Hand ataxia	10% (3/30) (2 ET, 1 ET-PD)	1–4 weeks
Related to stereotactic frame		
Scalp numbness	17% (5/30)	1–4 weeks
Haematoma near the eye	10% (3/30)	1–2 weeks

Abbreviations used: CRST, Clinical rating scale for tremor; DBS, deep brain stimulation; ET, essential tremor; MRgFUS, MRI-guided focused ultrasound ;PD, Parkinson's disease; PDQ-39 = PD Questionnaire; QUEST, quality of life in essential tremor; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale; VIM, ventral intermediate nucleus.

Study 6 Gallay M N (2016)

Details

Study type	**Case series**
Country	Switzerland
Recruitment period	Not reported
Study population and number	n=**21** consecutive patients with essential tremor
Age and sex	Mean 69 years; 71% (15/21) male
Patient selection criteria	ET with postural or kinetic components reaching an intensity of at least 3 over 4. Tremor resistance to pharmacological treatment or appearance of side effects of drugs preventing their use. Absence of dementia. Strongly diminished quality of life.
Technique	Magnetic resonance guided focused ultrasound cerebellothalamic tractotomy done in a 3-T MRI system (GE Discovery 750, GE Healthcare) using the ExAblate Neuro device (InSightec). When the procedure was done bilaterally, it was done first on the left, with a 1-year interval for the second side. The patients were fully awake during sonications. They had a mild anxiolytic (1.25–2.5 mg lorazepam) and gastric protection (pantoprazole 40 mg).
Follow-up	**1 year**
Conflict of interest/source of funding	None

Analysis

Follow-up issues:

- Postoperative follow-ups were done at 3 months and 1 year. For international patients (16/21), the 3-month assessment was done by correspondence with video recordings and drawing of spirals.
- In 2 patients (1 and 2), a complement of targeting was done on the already operated side during a second treatment session.

Study design issues:

- Primary relief assessment indicators were postoperative ETRS (Fahn, Tolosa, and Marin), hand function subscore (item 11–14 of ETRS, describing spiral and line drawings and pouring) presented for the targeted hand over 16 points (HF16) and for both hands over 32 points (HF32), handwriting (item 10 of ETRS), drawing of spirals, and estimation of global tremor relief by the patient (in percent). Spirals were drawn with both hands with and without support on table. The worst tremulous spirals were always used in pre- and postoperative scoring of ETRS.
- The evolution of 7 patients with HF32 above 28 points over 32 (group 1) differentiated itself from the others' (group 2) and was analysed separately.
- Global tremor relief estimations were provided by the patients.
- Lesion reconstruction and measurement of targeting accuracy were done on 2-day post-treatment MRI pictures for each CTT lesion.

Study population issues:

- The mean (±SD) disease duration was 29.9±15 years.
- The baseline tremor score on ETRS (0 to 144) was 57.6±13.2.
- 14% (3/21) of patients had bilateral treatment.

Other issues: Not reported.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 21

• Sufficient temperature was reached in every patient.
• The maximum applied energy was 30,800 J (mean 16,073, SD± 6,037), and the maximal power was 1250 W.
• The mean operation time from the stereotactic head frame fixation to the frame ablation was 4.45±1.1 h.

Essential tremor
<table>
<tr><th></th><th>ETRS (mean±SD)</th></tr>
<tr><td>Baseline (n=21)</td><td>57.6±13.2</td></tr>
<tr><td>1 year (n=10)</td><td>25.8±17.6 (55% reduction)</td></tr>
</table>
Regression analyses showed 2 significant predictors for functional improvement in the targeted hand: the preoperative ETRS (r2=0.32, F=8.75, and p<0.01) and HF32 (r2=0.34, F=9.35, p<0.01).
The higher the preoperative score, the lower the percentage of improvement of the dominant hand score.

Hand function (HF 16 – higher score indicating more severe tremor)
<table>
<tr><th></th><th>All patients (n=21)</th><th>Group 1 (n=7)</th><th>Group (n=14)</th></tr>
<tr><td>Baseline (mean±SD)</td><td>12.4± 3.3</td><td>15.3± 1.3</td><td>11.0±3.1</td></tr>
<tr><td>% improvement at 3 months</td><td>74%</td><td>41%</td><td>90%</td></tr>
<tr><td>% improvement at 1 year</td><td>78%</td><td>40%</td><td>90%</td></tr>
</table>
The 2 patients in group 1 treated bilaterally showed 75% and 88 % improvement of HF16 in their dominant hand and 78 % and 56% improvement of HF16 in their non-dominant hand 1 year after the treatment of the second side.
There was a highly statistically significant effect of the procedure on the HF16 score at 2 days, 3 months, and 1 year post-procedure (p<0.001).

Global tremor relief (mean patient estimation)
<table>
<tr><th></th><th>Global tremor relief</th></tr>
<tr><td>2 days (n=21)</td><td>92%</td></tr>
<tr><td>1 year (n=12)</td><td>77%</td></tr>
</table>
• Head tremor was found in 6/21 patients with a mean of 1.2± 0.57 (n=6) at baseline and 0.25± 0.2 (n=6) at 3 months.
• Preoperative postural tremor was found in 17/21 patients (mean 1.7±1.2). At the latest follow-up, only 1 patient showed a postural tremor (1–2 over 4) in the treated upper extremity.
</td><td>
Worsening of pre-existing gait instability with maximal worsening of 1 point over 4 (mean 0.7/4±0.3) : 24% (5/21)
At the last follow-up (3 months to 1 year), only 1 patient did not fully recover to his original walking ability and was 0.5 points worse than preoperatively.
</td></tr>
<tr><td colspan="2">Abbreviations used: ET, essential tremor; ETRS, essential tremor rating scale; HF, hand function; SD, standard deviation.</td></tr>
</table>

Study 7 Elias W J (2013)

Details

Study type	**Case series**
Country	United States
Recruitment period	2011
Study population and number	n=**15** patients with essential tremor
Age and sex	Mean 67 years; 67% (10/15) male
Patient selection criteria	Inclusion criteria: patients with severe (defined as a score of >2 on postural or action item on the CRST in the dominant hand and substantial disability in the performance of at least 2 daily activities from the disability subsection of the scale), medication-refractory (defined as persistent disabling tremor despite at least 2 trials of a full-dose therapeutic medication, 1 of which had to include propranolol or primidone) essential tremor. Exclusion criteria: patients who had had previous stereotactic or cranial surgery or who had other neurodegenerative conditions (including Parkinson's disease), unstable cardiac conditions, or a coagulopathy. All patients were screened by a neuropsychologist for the legal capacity to provide informed consent and to exclude cognitive impairment, a history of psychiatric disease, or previous evidence of substance abuse. Patients also had ultrasonography of the legs to rule out the presence of deep vein thrombosis.
Technique	The focused ultrasound thalamotomy was done in an MRI-guided focused ultrasound system, consisting of a 3 Tesla MRI (GE) and the ExAblate Neuro (InSightec), which includes a hemispheric, 650-kHz, 1024-element, phased-array transducer.
Follow-up	**1 year**
Conflict of interest/source of funding	All financial support was provided by the Focused Ultrasound Surgery Foundation. InSightec provided technical assistance for all the treatments and made financial contributions to the Focused Ultrasound Surgery Foundation.

Analysis

Follow-up issues: Patients were assessed at baseline and at 1 day, 1 week, 1 month, 3 months, and 12 months after treatment.

Study design issues:

- In each patient, the dominant hand was the most severely affected extremity and was targeted for treatment.
- All safety data was recorded and the effectiveness of tremor suppression was assessed using the CRST to calculate the total score (ranging from 0 to 160), hand subscore (primary outcome, ranging from 0 to 32), and disability subscore (ranging from 0 to 32), with higher scores indicating worse tremor. The patients' perceptions of treatment efficacy was assessed with the Quality of Life in Essential Tremor Questionnaire (ranging from 0 to 100%, with higher scores indicating greater perceived disability).

Study population issues:

- The mean history of tremor was 32.0±21.3 years (range, 4 to 60)**.**
- All tremors had been medically resistant to trials of a median of 2 medications (range 2 to 5).
- Six patients reported a beneficial tremor response after the consumption of 1 or 2 alcoholic drinks. Two patients had peripheral neuropathy at baseline.

Other issues: No comprehensive cognitive assessments were done and it is possible that focused ultrasound thalamotomy caused cognitive impairment.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **15**

Tremor (CRST score, mean±SD)

	Baseline	3 months	1 year	Change from baseline to 1 year
Contralateral hand tremor	20.4±5.2	4.3±3.5	5.2±4.8	75% (p=0.001)
Total tremor	54.9±14.4	-	24.3±14.8	56% (p=0.001)
Ipsilateral hand tremor	13.4±5.2		13.5±6.3	p=0.90

Among 10 patients who had axial tremor, there was improvement of at least 2 points in 6 patients, with no worsening of tremor, with mean changes ranging from 2.3 to 2.7 points (on a scale of 44 points) (p=0.26). Five of 9 vocal tremors improved partially but were not quantified with statistical analysis.

Disability (mean score±SD)

	Baseline	1 year	p value
Disability subsection of the CRST score	18.2±4.1	2.8±3.4	0.001

Physical Performance Test (mean score±SD, ranging from 0 to 32, with higher scores indicating better performance)

	Baseline	1 year	p value
Physical Performance Test score	22.9±3.0	27.1±2.7	0.001

Quality of life

	Baseline	1 year	p value
Quality of Life in Essential Tremor Questionnaire	37%	12%	0.001

Safety

Adverse events (n=15)

Event	Transient	1 year
Related to thalamotomy		
Paraesthesia: lip or tongue	60% (9/15)	13% (2/15)
Paraesthesia: finger	33% (5/15)	7% (1/15)
Dysesthesia of index finger[1]	7% (1/15)	7% (1/15)
"Unsteady" feeling	33% (5/15)	0
Ataxia (<1 month)	27% (4/15)	0
Dysmetria (<1 month)	7% (1/15)	0
Weak grip (5 days)	7% (1/15)	0
Slurred speech (1 day)	7% (1/15)	0
Related to use of stereotactic frame		
Headache >1 day	27% (4/15)	0
Scalp numbness in occipital region	27% (4/15)	0
Pin-site laceration	7% (1/15)	0
Periorbital oedema	7% (1/15)	0
Related to sonication[2]		
Head pain	60% (9/15)	0
"Flushed" or "warm" sensation	27% (4/15)	0
"Tilting," "falling," or "spinning" sensation	33% (5/15)	0
Light-headedness	40% (6/15)	0
Nausea	33% (5/15)	0
Emesis	20% (3/15)	0
Syncope	7% (1/15)	0
Related to MRI		
Scalp burn from pin-site heating	13% (2/15)	0

[1] Dysesthesia of the index finger was the only serious adverse event reported during the study.

[2] Sonication-related side effects were defined as those that occurred only during the 10 to 20 seconds of sonication and immediately resolved.

Abbreviations used: CRST, clinical rating scale for tremor; MRI, magnetic resonance imaging; SD, standard deviation

Study 8 Chang W S (2015)

Details

Study type	**Case series**
Country	Korea
Recruitment period	2012
Study population and number	n=**11** patients with essential tremor
Age and sex	Mean 65 years; 82% (9/11) male
Patient selection criteria	Inclusion criteria: confirmed medication-refractory ET, between 18 years and 80 years of age and a primary diagnosis of ET diagnosed by clinical history and examination by a movement disorder neurologist. Exclusion criteria: diagnosis of a current or past psychiatric illness, current substance abuse, other neurological disorders that affect brain function such as idiopathic Parkinson's disease, contraindications for MRI, and known intolerance or allergies to the MRI contrast agent.
Technique	Magnetic resonance guided focused ultrasound thalamotomy in a 3 T MRI system (GE medical system) using the ExAblate 4000 device (InSightec).
Follow-up	**6 months**
Conflict of interest/source of funding	This study was supported by a research grant from InSightec. InSightec was the regulatory sponsor of this study, and provided technical assistance.

Analysis
Follow-up issues:
- Tremor severity and functional impairment were assessed with the CRST at baseline and then at 1 week, 1 month, 3 months and 6 months after treatment.
- Adverse effects were sought and ascertained by directed questions and by neurological examination.
- Conventional 3 T MRIs (GE medical system) were serially done 1 day after the procedure or at 1 week, 1 month, 3 months and 6 months post-treatment.

Study design issues: Doses of medication for ET were stable for 30 days before enrolment and then maintained without adjustment during the study.
Study population issues: The symptom duration was 10 to 57 years before the procedure.
Other issues: Not reported.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>Number of patients analysed: 8

Procedure success: 73% (8/11)
• The procedure could only be considered complete in 8 of 11 patients because of inadequate increases in temperature (below 50°C).
• Skull volume and maximum temperature rise were linearly correlated (linear regression, p=0.003).

Tremor (mean CRST score)
<table>
<tr><th></th><th>Baseline</th><th>1 week</th><th>6 months</th><th>p value for the change from baseline to 6 months (non-parametric Wilcoxon test)</th></tr>
<tr><td>CRST part A</td><td>5.1</td><td>1.3</td><td>1.4</td><td>0.011</td></tr>
<tr><td>CRST part B</td><td>13</td><td>2.5</td><td>2.6</td><td>0.011</td></tr>
<tr><td>CRST part C (activity of daily living)</td><td>13.5</td><td>2.9</td><td>2.8</td><td>0.011</td></tr>
</table>
CRST Part A, 3 items: resting, postural, and action or intention components of hand tremor.
CRST Part B, 5 tasks involving handwriting, drawing, and pouring.</td><td>Vestibular symptoms such as dizziness, nausea and vomiting in the middle of sonications: 45% (5/11)

Transient mild balance problems due to oedema adjacent to the medial lemniscus: 1/11
This patient was prescribed oral corticosteroid therapy for 1 month.</td></tr>
<tr><td colspan="2">Abbreviations used: CRST, clinical rating scale for tremor; ET, essential tremor; MRI, magnetic resonance imaging.</td></tr>
</table>

Study 9 Lipsman N (2013)

Details

Study type	**Case series**
Country	Canada
Recruitment period	2012-13
Study population and number	n=**4** patients with essential tremor
Age and sex	Mean 71 years; 100% (4/4) male
Patient selection criteria	Inclusion criteria: aged between 18 and 80 years, able and willing to give consent and able to attend all study visits, a diagnosis of essential tremor, tremor refractory to adequate trials of at least 2 medications, one of which should be either propranolol or primidone. The VIM region of the thalamus must be apparent on MRI such that targeting can be done with either direct visualisation or by measurement from known anatomic landmarks, able to communicate sensations during treatment, postural or intention tremor severity score of 2 or more in the dominant hand or arm as measured by the CRST, stable doses of all medications for 30 days before study entry and for the duration of the study, substantial disability due to essential tremor despite medical treatment (CRST score of 2 or above in any one of the items on the disability subsection of the CRST). Exclusion criteria: unstable cardiac status, severe hypertension, contraindications for MRI, known intolerance or allergies to the MRI contrast agent, cerebrovascular disease, not able or willing to tolerate the needed prolonged stationary supine position during treatment, unable to communicate with the investigator and staff, presence of any other neurodegenerative disease, presence of significant cognitive impairment as determined by a score of 24 or less on the mini-mental state examination, history of seizures within the past year, brain tumours, psychiatric illnesses that are not well controlled, risk factors for intraoperative or postoperative bleeding or a documented coagulopathy, pregnancy or lactation, unable to provide consent for any reason, legal incapacity or limited legal capacity, previous deep brain stimulation or a prior stereotactic ablation of the basal ganglia.
Technique	Thalamotomy using a focused ultrasound transducer (650 kHz system, ExAblate Neuro, InSightec,) with simultaneous MRI.
Follow-up	**3 months**
Conflict of interest/source of funding	This study was funded by the Focused Ultrasound Foundation (Virginia, USA). InSightec (Haifa, Israel) was the regulatory sponsor of the study, providing technical assistance and assistance with regulatory requirements.

Analysis

Follow-up issues:

- Patients had neurological examination, tremor assessment, and structural MRI scanning at 1, 30, and 90 days after the procedure.
- No patients withdrew consent once it was obtained, and all patients completed all study visits.

Study design issues:

- Ten patients were screened, and 6 patients were excluded owing to age, minimal tremor severity, diagnosis other than essential tremor, or previous neurosurgery.
- Measured outcomes were tremor severity in the treated arm and functional impairment, and rates of adverse events.

Study population issues: The mean disease duration was 18 years.

Other issues: Not reported.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **4** **Tremor (CRST score)** There was a substantial improvement in tremor in all 4 patients during the sonications. The immediate benefits on tremor at the completion of the procedure were maintained at 1 month and 3 months. • Mean reduction in tremor score of the treated hand at 1 month: 89% • Mean reduction in tremor score of the treated hand at 3 months: 81% • Mean reduction in total impairment score on motor tasks at 1 month (part B of the CRST): 46% • Mean reduction in total impairment score on motor tasks at 3 months (part B of the CRST): 40% • Mean reduction in perceived functional disability related to tremor at 3 months (part C of the CRST): 51%.	• 2 patients developed **paraesthesias** during sonication, presumably related to lesion spread to afferent sensory axons or the sensory relay nucleus of the thalamus. In patient 1 they resolved after the completion of each sonication but in patient 2 they persisted, and the procedure was stopped. Patient 2 had paraesthesias in the tips of the thumb and index finger which persisted at the 3-month follow-up. • One patient developed a lower limb **deep vein thrombosis** around 1 week after the procedure, which needed anticoagulation treatment for 3 months. This event might have been related to the length of the procedure.
Abbreviations used: CRST, clinical rating scale for tremor; ET, essential tremor; MRI, magnetic resonance imaging.	

Study 10 Schreglmann S R (2017)

Details

Study type	**Prospective case series**
Country	Switzerland (single centre)
Recruitment period	Not reported
Study population and number	n=**6** patients with essential tremor
Age and sex	Mean 71 years; gender not reported
Patient selection criteria	Patients with essential tremor and insufficient symptom control.
Technique	Unilateral ablation of the cerebellothalamic tract by MRIgFUS using the Exablate Neuro system.
Follow-up	**6 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues:

- Motor symptoms, manual dexterity, cognition and quality of life were assessed before intervention, and at 48 hours, 1, 3 and 6 months after intervention.
- 2 patients were not available for the evaluations at 1 and 3 months but they attended all other evaluations.

Study design issues:

- The primary research question was to assess the efficacy and safety of unilateral MRIgFUS ablation of the cerebellothalamic tract in essential tremor.
- The primary endpoint was change in hand tremor severity.
- Rating of standardised video recordings was blinded for the evaluation by a movement disorder neurologist not involved in the treatments.

Study population issues:

- The mean disease duration was 25 years.
- One patient was taking propranolol at the time of the procedure.

Other issues: None.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **6**

Tremor (CRST score)

	Baseline	6 months	Absolute reduction	95% CI	p value
Overall tremor severity	43.8±9.8	19.8±6.8	24.0	18.1 to 29.9	<0.001
Unilateral hand score on the treated side	14.3±4.9	2.5±2.6	11.8	8.4 to 15.2	<0.001

Quality of life

	Baseline	6 months	Absolute reduction	95% CI	p value
QUEST score*	50.5±19.4	24.8±11.4	25.7	3.5 to 47.28	0.046

* Scale ranges from 0 to 100, with higher scores indicating greater perceived disability.

There were no statistically significant changes in manual dexterity (9-hole peg test) in the treated and non-treated hand, concentration and fine motor (Trail-Making Test A and B), and cognitive screening (Mini-mental state examination, Montreal cognitive assessment).

Safety

During the procedure

- **Vestibular symptoms**: 67% (4/6)
  They exclusively occurred during the final sonications that delivered the highest acoustic power per patient.

After the procedure

- **Subjective transient clumsiness of the treated hand**: 1/6
- **Gait instability**: 1/6
- **Objective tendency to veer to the treated side**: 1/6

These 3 complications resolved within 3 months.

- 1 of the patients had a fall at home 4 weeks after the procedure with an occipital fracture, intracranial haematoma and retrograde amnesia for the event, necessitating hospitalisation with eventual full recovery. Retrospect analysis revealed an unexplained fall 6 months before the intervention in this patient.

Abbreviations used: CI, confidence interval; CRST, clinical rating scale for tremor; MRIgFUS, MRI-guided focused ultrasound; QUEST, quality of life in essential tremor

Study 11 Schreglmann SR (2018)

Details

Study type	**Systematic review and meta-analysis**
Country	Not reported
Recruitment period	Studies published between 1990 and 2017
Study population and number	**Essential tremor indication only** Efficacy :n=**412 (79 MRIgFUS Vim versus 27 MRIgFUS CTT versus 254 Gamma knife versus 25 RF Vim)** patients with essential tremor Safety: n=**273 (82 MRIgFUS Vim versus 6 MRIgFUS CTT versus 153 Gamma knife versus 32 RF Vim)** patients with essential tremor
Age and sex	Not reported
Patient selection criteria	Inclusion criteria: Adult patients with a tremor diagnosis of confirmed aetiology; unilateral or bilateral lesional functional neurosurgical intervention in a central neuroanatomical structure. Study design: Randomised controlled trials, meta-analysis, case-control, prospective and retrospective case series; a minimum of 5 patients included per cohort; minimum follow-up of 2 months after the intervention. Peer-reviewed articles without language restriction. Studies reporting tremor outcome on a validated tremor scale and side effects after unilateral only interventions. Exclusion criteria: patients subjected to lesional functional neurosurgery in more than 1 anatomical structure at the same time or stimulation techniques (deep brain stimulation); studies reporting results from mixed aetiologies or mixed intervention; letters, abstracts and editorials; cohorts including bilateral interventions.
Technique	Incisional (placement of a stylette, leukotome, cryosurgery or radiofrequency probe after skull opening) or incisionless (transcranially focused ultrasound (MRI-guided focused ultrasound), radiation energy (Gamma Knife) procedure.
Follow-up	**Not reported**
Conflict of interest/source of funding	No competing interests declared.

Analysis
Follow-up issues: Follow-up time-points were not homogeneous between cohorts.
Study design issues:

- This work was conducted according to the recommendations from the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement.
- Primary outcome measure was the change in upper limb tremor severity from baseline to follow-up.
- To minimise selection/reporting bias if more than 1 follow-up time-point was reported, the time-point with the largest number of patients retained was included in the analysis. The standardised mean difference (Hedge's g) was used to calculate the effect size of the treatment effect.
- Pooled participant data from studies reporting pre-interventional and post-interventional tremor scores (mean±SD) were included in a random-effects meta-analysis using the Meta-Essentials workbook toolbox.
- Follow-up duration in months was imputed as a moderator and computed by univariate, weighted regression using a random effects model to control for an effect of follow-up duration on the effect size.
- Homogeneous cohorts (same tremor aetiology, intervention target and technique) were grouped together for subgroup analysis if they consisted of a minimum of n=2.
- After testing for normality, safety data were analysed using non-parametric Kruskal-Wallis test and Dunn's multiple comparison test where appropriate using GraphPad PRISM 6.
- Studies included in the meta-analysis were assessed according to standardised tools established for the grading of cohort studies (Newcastle Ottawa-Scale) and randomised controlled trials (Jadad-Scale).
- The authors noted that ''primary tremor data were heterogeneous in its use of rating scales, item and compound item sums.''

Other issues: The studies on MRIgFUS for essential tremor included in this systematic review and meta-analysis for efficacy were as follows: Gallay (2016), Schreglmann (2017), Elias (2013), Elias (2016) and Chang (2015). All are included in Table 2.

Key efficacy and safety findings

Efficacy

Number of patients analysed for efficacy: **n=412 (79 MRIgFUS Vim versus 27 MRIgFUS CTT versus 254 Gamma knife versus 25 RF Vim)**

Tremor reduction

	MRIgFUS CTT (n=27)	**MRIgFUS Vim** (n=79)	**RF Vim** (n=25)	**GK Vim** (n=254)
Mean tremor reduction, Hedge's g (95% CI)	-2.35 (-2.51 to -2.19) I^2= 0.00	-2.08 (-2.77 to -1.39) I^2=0.51	-2.42 (-5.26 to 0.43) I^2=0.85	-2.13 (-3.78 to -0.48) I^2=0.92

Mean effect on tremor was similar between groups (a negative effect size indicates improvement of tremor).

Across cohorts, duration of follow-up did not have a statistically significant influence on treatment effect size.

Safety

Number of patients analysed for safety: **n=273 (82 MRIgFUS Vim versus 6 MRIgFUS CTT versus 153 Gamma knife versus 32 RF Vim)**

Mean rates of persistent side effects after unilateral lesions in essential tremor

	MRIgFUS CTT (n=6)	**MRIgFUS Vim** (n=82)	**RF Vim** (n=32)	**GK Vim** (n=153)
Mean rates of persistent side effects (swallowing difficulties, sensory changes only)	0.0%±0.0%	18.7%±16.2%	9.3%±8.6%	1.8%±3.0%

There was no statistically significant difference between groups (χ^2=4.49, p=0.21).

Follow-up duration between studies differed statistically significantly on a group level (χ^2=7.46, p=0.02), but not on multiple comparisons.

Abbreviations used: CI, confidence interval; CTT, cerebellothalamic tract; MRIgFUS, MRI-guided focused ultrasound; RF, radiofrequency ablation; Vim, ventral intermediate nucleus

Validity and generalisability of the studies

- There was only 1 RCT included in table 2.[1, 2]
- The longest follow-up in the studies included in table 2 was 2 years.[2, 5]
- In 1 study included in table 2 the procedure targeted the posterior subthalamic area[6] instead of the ventral intermediate thalamus (VIM).
- In study 6, the procedure was done bilaterally using a non-VIM target.[6]

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Unilateral MRI-guided focused ultrasound thalamotomy for moderate-to-severe tremor in Parkinson's disease. NICE interventional procedure guidance 606 (2018). Available from https://www.nice.org.uk/guidance/ipg606
- Magnetic resonance image-guided transcutaneous focused ultrasound for uterine fibroids. NICE interventional procedure guidance 413 (2011). Available from http://www.nice.org.uk/guidance/IPG413
- Deep brain stimulation for tremor and dystonia (excluding Parkinson's disease). NICE interventional procedure guidance 188 (2006). Available from http://www.nice.org.uk/guidance/IPG188

Additional information considered by IPAC

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public

consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Four Specialist Adviser Questionnaires for unilateral MRI-guided focused ultrasound thalamotomy for treatment-resistant essential tremor were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Company engagement

A structured information request was sent to 1 company who manufacture a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

- Ongoing studies
  - A Feasibility Clinical Trial of the Magnetic Resonance Guided Focused Ultrasound (MRgFUS) for the Management of Treatment-Refractory Movement Disorders NCT02252380. Case series; Canada; Enrolment: 10; estimated completion date: December 2017.
  - Continued Access Protocol: ExAblate Transcranial MR Guided Focused Ultrasound for the Treatment of Essential Tremors NCT02289560. Case series; United States; Estimated Enrolment: 50; Estimated Primary Completion Date: December 2017.
  - ExAblate Transcranial MR Guided Focused Ultrasound for the Treatment of Essential Tremors NCT01827904. RCT; United States, Canada, Japan, Republic of Korea; Estimated Enrolment: 72; Estimated Completion Date: December 2017.
- Some patients may not be able to have MRI.

References

1. Elias W J, Lipsman N, Ondo W G et al. (2016) A Randomized Trial of Focused Ultrasound Thalamotomy for Essential Tremor. New England Journal of Medicine 375(8), 730-9
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3. Kim M, Jung N Y, Park C K, et al. (2017) Comparative Evaluation of Magnetic Resonance-Guided Focused Ultrasound Surgery for Essential Tremor. Stereotactic & Functional Neurosurgery 95(4), 279-286
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5. Zaaroor M, Sinai A, Goldsher D et al. (2017) Magnetic resonance-guided focused ultrasound thalamotomy for tremor: a report of 30 Parkinson's disease and essential tremor cases. J Neurosurg, 1-9
6. Gallay Marc N, Moser David, Rossi Franziska et al. (2016) Incisionless transcranial MR-guided focused ultrasound in essential tremor: cerebellothalamic tractotomy. Journal of Therapeutic Ultrasound 4, 5
7. Elias W J, Huss D, Voss T et al. (2013) A pilot study of focused ultrasound thalamotomy for essential tremor. New England Journal of Medicine 369(7), 640-8
8. Chang W S, Jung H, Kweon E J et al. (2015) Unilateral magnetic resonance guided focused ultrasound thalamotomy for essential tremor: practices and clinicoradiological outcomes. Journal of Neurology, and Neurosurgery & Psychiatry 86(3), 257-64
9. Lipsman N, Schwartz M L, Huang Y et al. (2013) MR-guided focused ultrasound thalamotomy for essential tremor: a proof-of-concept study. Lancet Neurology 12(5), 462-8
10. Schreglmann S R, Bauer R, Hagele-Link S et al. (2017) Unilateral cerebellothalamic tract ablation in essential tremor by MRI-guided focused ultrasound. Neurology 88(14), 1329-1333
11. Schreglmann S R, Krauss J K, Chang J W et al. (2018) Functional lesional neurosurgery for tremor: a systematic review and meta-analysis. Journal of Neurology, and Neurosurgery & Psychiatry; 1-10

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	04/03/2018	Issue 3 of 12, March 2018
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	04/03/2018	Issue 2 of 12, February 2018
HTA database (Cochrane Library)	04/03/2018	Issue 4 of 4, October 2016
MEDLINE (Ovid)	04/03/2018	1946 to Present with Daily Update
MEDLINE In-Process (Ovid) & MEDLINE Epubs ahead of print (Ovid)	04/03/2018	March 02, 2018
EMBASE (Ovid)	04/03/2018	1974 to 2018 Week 10

Trial sources searched on 08/12/2016

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched on 08/12/2016

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 Parkinson Disease/

2 Parkinsonian Disorders/

3 Tremor/ or Essential Tremor/

4 Movement Disorder/

5 parkinson*.tw.

6 tremor*.tw.

7 (movement* adj4 disord*).tw.

8 (Paralysis adj4 agitans).tw.

9 (shaking palsy or shaking palsies).tw.

10 or/1-9

11 Magnetic Resonance Imaging/

12 MAGNETIC RESONANCE IMAGING, INTERVENTIONAL/

13 MRI.tw.

14 ((MR or magnet*) adj4 (guid* or imag*)).tw.

15 (magnet* adj4 resonanc*).tw.

16 or/11-15

17 Ultrasonography, Interventional/

18 exp Ultrasonic Therapy/

19 High-Intensity Focused Ultrasound Ablation/

20 (focus* adj4 (ultraso* or ultra-so*)).tw.

21 (focus* adj4 acoustic* adj4 energy*).tw.

22 ((ultraso* or ultra-so*) adj4 (therap* or surg* or ablat*)).tw.

23 ((ultraso* or ultra-so*) adj4 thalamotom*).tw.

24 (ultrasonograph* adj4 intervention*).tw.

25 HIFU.tw.

26 thermoablat*.tw.

27 (therm* adj4 ablat*).tw.

28 or/17-27

29 10 and 16 and 28

30 (MRgFUS or MRgHIFU).tw.

31 29 or 30

32 exablate.tw.

33 31 or 32

34 animals/ not humans/

35 33 not 34

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Chazen J L, Sarva H, Stieg P E et al. (2017) Clinical improvement associated with targeted interruption of the cerebellothalamic tract following MR-guided focused ultrasound for essential tremor. J Neurosurg, 1-9	Case reports n=4 FU=1 day	All patients had excellent postoperative tremor control and successful pre- and post-procedural DTI fibre tracking of the corticospinal tract, medial lemniscus, and DRT. Immediate post-procedure DTI failed to track the DRT ipsilateral to the lesion site with a preserved contralateral DRT, coincident with substantial resolution of contralateral tremor.	Studies with more patients or longer follow-up are included.
Federau C, Goubran M, Rosenberg J et al. (2017) Transcranial MRI-guided high-intensity focused ultrasound for treatment of essential tremor: A pilot study on the correlation between lesion size, lesion location, thermal dose, and clinical outcome. Journal of Magnetic Resonance Imaging 27	Case series n=8 FU=1 year	In this pilot study a good correlation was found between the size of the lesion, the thermal dose, and the clinical outcome in patients treated for essential tremor with ablation of the ventral lateral posterior thalamic nucleus with tcMRgFUS.	Studies with more patients or longer follow-up are included.
Fishman P S, Elias W J, Ghanouni P et al. (2018) Neurological adverse event profile of magnetic resonance imaging-guided focused ultrasound thalamotomy for essential tremor. Movement Disorders doi: 10.1002/mds.27401. [Epub ahead of print]	Analysis of safety data n=186 patients from 5 studies	Procedure-related serious adverse events were very infrequent (1.6%), without intracerebral haemorrhages or infections. Adverse events were usually transient and were commonly rated as mild (79%) and rarely severe (1%). As previously reported, abnormalities in sensation and balance were the commonest thalamotomy-related adverse events.	3 of the studies included in this review are included in Table 2. The other 2 studies are unpublished and do not appear to report any significant adverse events that were considered to be related to the procedure.
Giugno Antonella, Maugeri Rosario, Graziano Francescaet al. (2017) Restoring Neurological Physiology: The Innovative Role of High-Energy MR-Guided Focused Ultrasound (HIMRgFUS). Preliminary Data from a New	Case series n=2 FU=5 and 7 months	In both patients, the treatment completely abolished the tremor on the treated side, with results being excellent and stable after 7 and 5 months respectively; no side effects were encountered.	Larger studies or studies with longer follow-up are already included in table 2

Method of Lesioning Surgery. Acta Neurochirurgica - Supplement 124, 55-59			
Harary M, Essayed W I, Valdes P A et al. (2018) Volumetric analysis of magnetic resonance-guided focused ultrasound thalamotomy lesions. Neurosurgical Focus 44(2), E6	Case series n=7 FU=1 year	MRgFUS thalamotomy demonstrates sustained clinical efficacy at 1 year for the treatment of medication-refractory ET. This technology can create accurate, predictable, and small-volume lesions that are stable over time. Instances of AEs are transient and are associated with the pattern of perilesional oedema expansion. Additional analysis of a larger MRgFUS thalamotomy cohort could provide more information to maximize clinical effect and reduce the rate of long-lasting AEs.	Studies with more patients or longer follow-up are included.
Rohani M, and Fasano A (2017) Focused Ultrasound for Essential Tremor: Review of the Evidence and Discussion of Current Hurdles. Tremor and Other Hyperkinetic Movements 7, 462	Review Search date: January 2017	Studies have shown the safety and effectiveness of unilateral MRgFUS-thalamotomy in the treatment of ET. It has been successfully used in a few patients with Parkinson's disease-related tremor, and in fewer patients with fragile X-associated tremor/ataxia syndrome. The safety and long-term effects of the procedure are still unclear, as temporary and permanent adverse events have been reported as well as recurrence of tremor.	Narrative review.
Wang T R, Dallapiazza R F, Moosa S, Huss D et al. (2018) Thalamic Deep Brain Stimulation Salvages Failed Focused Ultrasound Thalamotomy for Essential Tremor: A Case Report. Stereotactic & Functional Neurosurgery 12	Single case report FU=6 months	This case demonstrates that thalamic DBS can salvage a failed FUS thalamotomy and also the feasibility of stimulating a previously lesioned target.	Studies with more patients or longer follow-up are included.
Wintermark M, Druzgal J, Huss D S et al. (2014) Imaging findings in MR imaging-guided focused ultrasound treatment for patients with essential tremor. Ajnr: American Journal of Neuroradiology 35(5), 891-6	Prospective case series n=15 FU=3 months	MRI-guided focused sonography can accurately ablate a precisely delineated target, with typical imaging findings seen in the days, weeks, and months following the treatment. Tremor control was optimal early when the lesion size and perilesional oedema were maximal and was less later when the perilesional oedema had resolved.	Same patients as in the Elias (2013) study which is included in Table 2.
Wintermark M, Huss D S, Shah B et al. (2014) Thalamic connectivity in patients with	Prospective case series	DT MRI after MRI-guided focused ultrasound thalamotomy depicts changes	Same patients as in the Elias (2013) study

essential tremor treated with MR imaging-guided focused ultrasound: in vivo fiber tracking by using diffusion-tensor MR imaging. Radiology 272(1), 202-9	n=14 FU=3 months	in specific brain structures. The magnitude of the DT imaging changes after thalamic lesion inducement correlates with the degree of clinical improvement in essential tremor.	which is included in Table 2.