NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of 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 the delivery of focused ultrasound to destroy a specific area of the brain (thalamus) under MRI guidance. The aim is to reduce the patient's tremor.

Contents

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.

Procedure name

- MRI-guided focused ultrasound 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 and radiofrequency thalamotomy.

What the procedure involves

This procedure is carried out with the patient lying supine inside an MR 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 MR imaging 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 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, unlike deep brain stimulation, it can only be 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

Tremor

In a randomised controlled trial of 76 patients with essential tremor comparing MRI-guided focused ultrasound 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 case series of 21 patients with essential tremor treated by 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.[2]

In a case series of 15 patients with essential tremor treated by MRI-guided focused ultrasound 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).[3]

In a case series of 11 patients (results from 8 patients analysed) with essential tremor treated by MRI-guided focused ultrasound 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).[4]

In a case series of 4 patients with essential tremor treated by MRI-guided focused ultrasound 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).[5]

Functional activities of daily living

In the randomised controlled trial 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 MRI-guided focused ultrasound thalamotomy group than in the sham group at 3 months (62% compared with 3%, p<0.001).[1]

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).[3]

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).[5]

Quality of life

In the randomised controlled trial 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 case series of 15 patients, the QUEST score statistically significantly improved from 37% to 12% at 1 year (p=0.001).[3]

Safety summary

Safety events reported during the procedure

In a randomised controlled trial of 76 patients with essential tremor comparing MRI-guided focused ultrasound 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]

Head discomfort or pain

Head discomfort ('heat' or 'pressure') was reported in 30% (17/56) of patients in the MRI-guided focused ultrasound thalamotomy group and in none of the patients in the sham group (n=20) in the randomised controlled trial of 76 patients within 1 year of the procedure (p value not reported).[1]

Head pain that occurred only during sonication was reported in 60% (9/15) of patients in the case series of 15 patients.[3]

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 randomised controlled trial 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]

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.[3]

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.[4]

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 randomised controlled trial 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 randomised controlled trial 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 randomised controlled trial of 76 patients within 1 year of the procedure (p value not reported). [1]

Flushing or a warm sensation

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. [3]

Fainting

Fainting that occurred only during sonication was reported in 1 patient in the case series of 15 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 randomised controlled trial 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 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). [3]

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.[5]

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.[3]

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 randomised controlled trial of 76 patients within 1 year of the procedure (p value not reported). [1]

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 randomised controlled trial 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]

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 treated by 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.[2]

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.[3]

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.[4]

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 randomised controlled trial 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.[3]

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 randomised controlled trial of 76 patients within 1 year of the procedure (p value not reported).[1]

Weak grip, which lasted for 5 days after the procedure, was reported in 1 patient in the case series of 15 patients.[3]

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 randomised controlled trial of 76 patients within 1 year of the procedure (p value not reported).[1]

Slurred speech, which lasted for 1 day after the procedure was reported in 1 patient in the case series of 15 patients.[3]

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 randomised controlled trial 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 randomised controlled trial 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 randomised controlled trial of 76 patients within 1 year of the procedure (p value not reported).[1]

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 randomised controlled trial 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 randomised controlled trial 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 randomised controlled trial 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.[5]

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 randomised controlled trial of 76 patients within 1 month of the procedure (p value not reported).[1]

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.[3]

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 MRI-guided focused ultrasound thalamotomy for treatment-resistant essential tremor. The following databases were searched, covering the period from their start to 7 March 2017: 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 appendix C 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	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 127 patients from 1 randomised controlled trial [1] and 4 case series[2-5].

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 appendix A.

Table 2 Summary of key efficacy and safety findings on 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 receiving 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 treated by 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	-

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

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)
Vomiting	4% (2)							
Scalp tingling	7% (4)							5% (1)

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).

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 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 MR imaging 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 received 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 MR 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 3 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 4 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><td>Efficacy</td><td>Safety</td></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 steroid 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 5 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.	

Validity and generalisability of the studies

- There was only 1 randomised controlled trial included in table 2.[1]
- The longest follow-up in the studies included in table 2 was 1 year.[1-3]
- In 1 study included in table 2 the procedure targeted the posterior subthalamic area[2] instead of the ventral intermediate thalamus (VIM).
- In study 2, the procedure was done bilaterally using a non-VIM target.[2]

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

- MRI-guided focused ultrasound thalamotomy for moderate-to-severe tremor in Parkinson's disease. NICE interventional procedure guidance XXX (2017). Available from
- 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 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
2. 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
3. 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
4. Chang W S, Jung H 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
5. 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

Additional relevant papers

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
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 Method of Lesioning Surgery. Acta Neurochirurgica - Supplement 124, 55-59	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
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	MR imaging-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 B et al. (2014) Thalamic connectivity in patients with essential tremor treated with MR imaging-guided focused ultrasound: in vivo fiber tracking by using diffusion-tensor MR imaging. Radiology 272(1), 202-9	Prospective case series n=14 FU=3 months	DT MR imaging after MR imaging-guided focused ultrasound thalamotomy depicts changes 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.	Same patients as in the Elias (2013) study which is included in Table 2.

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane)	07/03/2017	Issue 3 of 12, March 2017
HTA database (Cochrane)	07/03/2017	Issue 4 of 4, October 2016
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane)	07/03/2017	Issue 2 of 12, February 2017
MEDLINE (Ovid)	07/03/2017	1946 to February Week 3 2017
MEDLINE In-Process (Ovid)	07/03/2017	February 27, 2017
EMBASE (Ovid)	07/03/2017	1974 to 2017 Week 09
PubMed	07/03/2017	n/a
BLIC (British Library)	07/03/2017	n/a

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