

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of unilateral MRI-guided focused ultrasound thalamotomy for moderate to severe tremor in Parkinson's disease

Parkinson's disease affects the brain and causes progressive symptoms, including tremor, which may be disabling. This procedure uses a special head frame that allows the delivery of focused ultrasound to a specific area of the brain (thalamus) under MRI guidance. The aim is to reduce the patient's tremor.

Contents

[Introduction](#)

[Description of the procedure](#)

[Efficacy summary](#)

[Safety summary](#)

[The evidence assessed](#)

[Validity and generalisability of the studies](#)

[Existing assessments of this procedure](#)

[Related NICE guidance](#)

[Additional information considered by IPAC](#)

[References](#)

[Additional relevant papers](#)

[Literature search strategy](#)

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 October 2017.

Procedure name

- Unilateral MRI-guided focused ultrasound thalamotomy for moderate to severe tremor in Parkinson's disease

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***

Parkinson's disease is a progressive neurodegenerative disease characterised by gradually worsening tremor, muscle rigidity and difficulties with starting and stopping movements. The tremor in Parkinson's disease occurs at rest and becomes less prominent with voluntary movement. It typically occurs first in the distal upper extremities then moves proximally and spreads to affect other parts of the body over time.

Treatment for Parkinson's disease include supportive therapies and medications such as levodopa, dopamine agonists and monoamine oxidase B inhibitors.

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 MRI scanner. The patient's head is shaved and a stereotactic head frame is attached. Patients are kept awake so they can report any of 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, unlike deep brain stimulation, it can only be done on 1 side.

Outcome measures

Unified Parkinson Disease Rating Scale (UPDRS)

UPDRS is used to assess symptoms associated with Parkinson's disease. It consists of: mentation, behaviour and mood (I); activities of daily living (II); motor examination (III); complications of therapy (IV); modified Hoehn and Yahr staging (V); and the Schwab and England scale (VI). The questions can be answered in the on or off state. Lower scores are better.

Efficacy summary

Tremor

In a case series of 13 patients with Parkinson's disease treated by unilateral MRI-guided focused ultrasound pallidothalamic tractotomy, the mean UPDRS score had changed from 38.7 at baseline to 21.1 at 3-month follow-up (p value not reported).¹

In a case series of 7 patients with Parkinson's disease treated by unilateral MRI-guided focused ultrasound thalamotomy, the mean \pm standard deviation (SD) UPDRS score had statistically significantly improved from 37.4 ± 12.2 at baseline to 18.8 ± 11.1 at 1 week ($p=0.007$). Item 20 (rest tremor in the treated side) and item 21 (action tremor in the treated side) of the UPDRS had both statistically significantly improved from 2.7 ± 1.1 and 3.0 ± 1.0 respectively to 0.0 ± 0.0 ($p < 0.001$). The effects were sustained within a mean follow-up of 7.3 months.²

In a case series of 30 patients, including 9 patients with Parkinson's disease-related tremor and 3 patients with essential tremor who developed Parkinson's disease many years later, the mean (\pm SD) score of the motor part of the UPDRS statistically significantly decreased from 24.9 ± 8.0 to 13.4 ± 9.2 after 6 months in the patients with Parkinson's disease ($p=0.009$). In the same patient group, item 20 and item 21 of the UPDRS had both statistically significantly improved from 2.90 ± 0.99 and 3.00 ± 1.16 to 0.3 ± 0.5 and 0.6 ± 1.1 respectively ($p < 0.001$).³

In a case series of 6 patients, including 3 patients with Parkinson's disease, all patients achieved a statistically significant, immediate and sustained 53%

improvement of the lateralised items of the tremor rating scale of contralateral hemibody 6 months after the procedure ($p < 0.05$, score at baseline was 17.0 ± 2.7). In the same study, in the patients with Parkinson's disease ($n=3$), the mean (\pm SD) scores of the activities of daily living and of the motor sections of the UPDRS did not statistically significantly changed.⁴

In a randomised controlled trial (RCT) of 27 patients comparing MRI-guided focused ultrasound thalamotomy ($n=20$) to sham ($n=7$), the tremor subscore (clinical rating scale for tremor [CRST] A+B) of the treated hand statistically significantly improved by a median 62% (interquartile range [IQR] 22.0% to 79.0%) from 17 points at baseline at 3 months in the treatment group compared with a 22% (-11.0% to 29.0%) improvement from 23 points at baseline in the sham group ($p=0.04$). In the same study, items 20 and 21 of the UPDRS improved by 1.5 and 1.0 points respectively in the treatment group compared with no improvement in the sham group (level of statistical significance not stated). The motor part score of the UPDRS improved by 8 points from 23 points at baseline at 3 months in the treatment group compared with a 1-point improvement from 25 points at baseline in the sham group (level of statistical significance not stated).⁵

Functional activities of daily living

In the case series of 7 patients, based on the clinical assessment by the examiner and patients, disability improved from severe to no functional disability immediately after the procedure and during follow-up.²

In the RCT of 27 patients, the median (IQR) CRST disability (part C) score improved by 7.5 (1.0 to 12.5) points after 3 months in the treatment group compared with 3.0 (0.0 to 4.0) points in the sham group (level of statistical significance not stated).⁵

Quality of life

In the case series of 7 patients, the mean Parkinson's Disease Questionnaire (PDQ)-39 score had statistically significantly decreased from 42.3 ± 16.4 at baseline to 21.6 ± 10.8 at 1 week ($p=0.008$), and this was sustained during the mean follow-up of 7.3 months.²

In the case series of 30 patients, the mean PDQ-39 score had statistically significantly decreased from 38.6 ± 16.8 at baseline to 20.6 ± 8.8 at 6 months in the patients with Parkinson's disease ($n=9$, $p=0.008$). The improvement in quality of life was sustained in 78% of the patients with Parkinson's disease and 66% of the patients with essential tremor who later developed Parkinson's disease ($n=2$).³

In the RCT of 27 patients, the median (IQR) PDQ-39 score improved by 5.4 (-2.4 to 11.9) points after 3 months in the treatment group compared with 7.6 (0.9 to 13.0) points in the sham group (level of statistical significance not stated).⁵

Antiparkinsonian medication

In the case series of 13 patients, the mean L-dopa equivalent doses changed from 827 mg/day at baseline to 536 mg/day at 3-month follow-up.¹

In the RCT of 27 patients, the median (IQR) levodopa-equivalent daily dosage were similar to baseline scores in both groups 3 months after the procedure.⁵

Neuropsychological outcomes

In the RCT of 27 patients, the Montreal cognitive assessment and Beck depression inventory scores were similar to baseline scores in both groups 3 months after the procedure.⁵

Recurrence of tremor

In the case series of 7 patients, re-emergence of short-lasting mild tremor was reported in 43% (3/7) of patients 1 week (n=1), 1 month (n=1) and 6 months (n=1) after the procedure.²

In the case series of 30 patients, tremor recurrence during the first 6 months after the procedure was reported in 22% (2/9) of patients with Parkinson's disease and in 67% (2/3) of patients with essential tremor who later developed Parkinson's disease.³

Safety summary

Head discomfort or pain

Headache during sonications was reported in 43% (3/7) of patients in a case series of 7 patients with Parkinson's disease.²

Headache during sonications was reported in 37% (11/30) of patients in a case series of 30 patients including 9 patients with Parkinson's disease-related tremor and 3 patients with essential tremor who developed Parkinson's disease many years later. It resolved within seconds to minutes. In the same study, burning scalp sensation during sonications was reported in 10% (3/30) of patients; it resolved within seconds.³

Local pain or burning, which were transient, were reported in 2 out of 3 patients with Parkinson's disease in a case series of 6 patients. In the same study, transient headache was reported in 1 out of 3 patients with Parkinson's disease.⁴

Scalp numbness, which was transient, was reported in 1 patient in the treatment group (n=20) and in none of the patients in the sham group (n=7) in the RCT of 27 patients. In the same study, transient headache was reported in 60% (12/20) of patients in the treatment group and in 43% (3/7) of patients in the sham group.

Head pain or heat sensation were reported in 15% (3/20) of patients in the treatment group and in none of the patients in the sham group. Pin site pain was reported in 1 patient in the treatment group and in 2 patients in the sham group,⁵

Vestibular symptoms

Dizziness during sonications was reported in 29% (2/7) of patients in the case series of 7 patients. In the same study, vertigo during sonications was reported in 57% (4/7) of patients.²

Dizziness during sonications was reported in 13% (4/30) of patients in the case series of 30 patients. It resolved within seconds to minutes. In the same study, vertigo during sonications was reported in 47% (14/30) of patients; it resolved within seconds. Nausea was reported in 10% (3/20) of patients and vomiting in 7% (2/30); they resolved within minutes.³

Dizziness, which was transient, was reported in 1 out of 3 patients with Parkinson's disease in the case series of 6 patients.⁴

Dizziness or vertigo, which were transient, were reported in 40% (8/20) of patients in the treatment group and in 14% (1/7) of patients in the sham group in the RCT of 27 patients. In the same study, stomach pain, or nausea or emesis were reported in 20% (4/20) of patients in the treatment group and in 1 patient in the sham group. Light headedness was reported in 2 patients in the treatment group and in none of the patients in the sham group.⁵

Hemiparesis

Hemiparesis, which was persistent, was reported in 1 out of 3 patients with Parkinson's disease in the case series of 6 patients.⁴

Hemiparesis was reported to be transient in 10% (2/20) of patients and persistent in 10% (2/20) of patients in the treatment group in the RCT of 27 patients.⁵

Paraesthesia or numbness

Lip paraesthesia during sonications was reported in 1 patient in the case series of 7 patients. It resolved after the target was repositioned 1 mm anteriorly.²

Lip paraesthesia during sonications was reported in 7% (2/30) of patients in the case series of 30 patients. It resolved within seconds.³

Scalp numbness was reported in 17% (5/30) of patients in the case series of 30 patients. It resolved within 1 to 4 weeks.³

Persistent numbness or paraesthesia were reported in 1 out of 3 patients with Parkinson's disease in the case series of 6 patients.⁴

Eyelid weakness, which was transient, was reported in 1 out of 3 patients with Parkinson's disease in the case series of 6 patients.⁴

Finger paraesthesia was reported as a transient adverse event in 35% (7/20) of patients and as a persistent adverse event in 1 patient in the treatment group in the RCT of 27 patients. In the same study, in the treatment group, orofacial paraesthesia was reported to be transient in 1 patient and persistent in 20% (4/20) of patients.⁵

Taste disturbance

Reduced ability to taste was reported in 1 patient in the case series of 7 patients.²

Taste disturbance was reported in 13% (4/30) of patients in the case series of 30 patients; it resolved within 1 to 3 months.³

Gait disturbance

Subjective unsteady feeling when walking was reported in 1 patient in the case series of 7 patients, which resolved (no further details reported). In the same study, tandem gait disturbance was reported in 1 patient; it resolved at 2-month follow-up.²

Gait ataxia after the procedure was reported in 1 patient with Parkinson's disease (n=9) and in 1 patient with essential tremor who later developed Parkinson's disease (n=3) in the case series of 30 patients. It resolved within 1 to 3 months. In the same study, unsteady feeling was reported in 13% (4/30) of patients; it resolved within 1 to 4 weeks.³

Ataxia was reported to be transient in 40% (4/20) of patients and persistent in 1 patient in the treatment group in the RCT of 27 patients. In the same study, dysmetria which was transient, was reported in 1 patient after the procedure.⁵

Hand ataxia

Hand ataxia after the procedure was reported in 1 patient with essential tremor who later developed Parkinson's disease (n=3) in the case series of 30 patients; it resolved within 1 to 4 weeks.³

Dysarthria

Dysarthria, which was transient, was reported in 1 out of 3 patients with Parkinson's disease in the case series of 6 patients.⁴

Haematoma

Haematoma near the eye was reported in 10% (3/30) of patients in the case series of 30 patients; it resolved within 1 to 2 weeks.³

Right-sided ecchymosis was reported in 1 patient in the treatment group and in none of the patients in the sham group in the RCT of 27 patients.⁵

Asthenia

Asthenia after the procedure was reported in 13% (4/30) of patients in the case series of 30 patients; it resolved within 1 to 4 weeks.³

Vocal change

Vocal change, which was mild and persistent, was reported in 1 patient out of 20 after the procedure in the RCT of 27 patients.⁵

Neck or back or shoulder pain

Neck or back or shoulder pain was reported in 20% (4/20) of patients in the treatment group compared with 1 patient in the sham group in the RCT of 27 patients.⁵

Decline in mental status

Decline in mental status was reported in 1 patient in the treatment group compared with none of the patients in the sham group in the RCT of 27 patients.⁵

Periorbital swelling

Periorbital swelling was reported in 10% (2/20) of patients in the treatment group compared with none of the patients in the sham group in the RCT of 27 patients.⁵

Spot in visual field

A spot in the visual field was reported in 1 patient in the treatment group and in none of the patients in the sham group in the RCT of 27 patients.⁵

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 MRI-guided focused ultrasound thalamotomy for moderate to severe tremor in Parkinson's disease. The following databases were searched, covering the period from their start to 24 October 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 moderate to severe tremor in Parkinson's disease.
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 62 patients from 1 RCT⁵ and 4 case series.¹⁻⁴

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 unilateral MRI-guided focused ultrasound thalamotomy for moderate to severe tremor in Parkinson's disease**Study 1 Magara A (2014)****Details**

Study type	Case series
Country	Switzerland
Recruitment period	2011
Study population and number	n= 13 consecutive patients with Parkinson's disease
Age and sex	Mean 64.5 years; 62% (8/13) male
Patient selection criteria	Inclusion criteria: Idiopathic PD as defined primarily by the presence of tremor at rest, hypobradikinesia, and rigidity. At least 1 of the 2 clinically most relevant symptoms, tremor at rest and akinesia, reached an intensity of at least 3/4. Symptoms have resisted to optimal pharmacological treatment including L-dopa and other antiparkinsonian drugs for at least 1 year. Absence of dementia. Strongly diminished quality of life.
Technique	<ul style="list-style-type: none"> • The treatment was done in a 3 Tesla (T) MRI system (GE Discovery 750, GE Healthcare) using the ExAblate Neuro device (InSightec). • The patients were fully awake and responsive during all the stages of the intervention. The medications administered before the procedure were sublingual lorazepam 1.25–2.5 mg and a gastric protection (pantoprazole 40 mg). • During the entire series of sonications, the patients were examined and questioned repeatedly to ensure their neurological integrity. • The pallidothalamic tractotomy was done unilaterally.
Follow-up	3 months
Conflict of interest/source of funding	The study was supported partially by InSightec Ltd, Rodiag Diagnostics Centers AG, and GE Medical Systems.

Analysis

Follow-up issues: Postoperative follow-up examinations and assessments were done at 3 months by 2 neurologists not affiliated with the treating neurosurgical centre.

Study design issues:

- The patients were assessed by complete neurological examinations and the filling of the Unified Parkinson Disease Scale, the Mini-Mental State Test (MMST), and the Hospital Anxiety and Depression Score (HADS).
- Primary relief assessment indicators were the postoperative reduction of the UPDRS score and the postoperative patient estimation of global symptom relief (GSR in percent).

Study population issues: The mean disease duration was 10 years.

Other issues: Not reported.

Key efficacy and safety findings

Efficacy	Safety
<p>Number of patients analysed: 13</p> <p>Unified Parkinson Disease Rating Scale (mean score, maximum 147)</p> <ul style="list-style-type: none"> • Baseline: 38.7 • 3-month follow-up: 21.1 <p>Mini-Mental State Test (mean score, maximum 30)</p> <ul style="list-style-type: none"> • Baseline: 29 • 3-month follow-up: 29.4 <p>Hospital Anxiety and Depression Score (mean score, maximum 42)</p> <ul style="list-style-type: none"> • Baseline: 14.1 • 3-month follow-up: 13 <p>Antiparkinsonian medication (mean L-dopa equivalents, mg/day, n=11)</p> <ul style="list-style-type: none"> • Baseline: 827 • 3-month follow-up: 536 <p>2 patients had stopped their L-dopa intake long before the intervention.</p> <p>The first 4 patients had a PTT using the lesional parameters applied for thalamotomies. They experienced recurrences at 3 months (mean UPDRS relief 7.6%, mean global symptom relief 22.5%), and their MRI showed no sign of thermal lesion in T2-weighted (T2w) images.</p> <p>As a consequence, the treatment protocol was adapted for the following 9 patients by applying repetition of the final temperatures 4 to 5 times. That produced thermocoagulations of larger volumes (172 mm³ against 83 mm³ for the first 4 patients), which remained visible at 3 months on T2w images. These 9 patients enjoyed a mean UPDRS reduction of 60.9% and a GSR of 56.7%.</p>	<p>There were no procedure- or device-related neurological side effects</p>
<p>Abbreviations used: GSR, Global symptom relief PD, Parkinson's disease; PTT, pallidothalamic tractotomy; UPDRS, Unified Parkinson Disease Rating Scale.</p>	

Study 2 Schlesinger I (2015)

Details

Study type	Case series
Country	Israel
Recruitment period	Not reported
Study population and number	n=7 patients with Parkinson's disease
Age and sex	Mean 59 years; 86% (6/7) male
Patient selection criteria	<p><u>Inclusion criteria</u>: Patients with Parkinson's disease and severe refractory tremor. The diagnosis of idiopathic Parkinson's disease was made according to the UK brain bank criteria. Severe refractory tremor was defined as a disabling tremor despite ample treatment trials with anticholinergic and dopaminergic medication.</p> <p><u>Exclusion criteria</u>: significant cognitive decline, current anticoagulant therapy, brain tumours or vascular malformation, significant unstable medical conditions, and contraindications for MR.</p>
Technique	<p>Unilateral MRI-guided Focused Ultrasound ventral intermediate nucleus thalamotomy using a 3-Tesla MRI (GE) and a focused ultrasound system (ExAblateNeuro, InSightec).</p> <p>Treatment included a gradual increase in total energy either by an increased intensity or by longer sonication durations. Sonications were stopped when adequate control of tremor was achieved, with the temperature reaching no more than 59°C.</p>
Follow-up	Mean 7 months
Conflict of interest/source of funding	The authors had no financial disclosures or conflict of interests.

Analysis

Follow-up issues: Not reported.

Study design issues:

- Severity of tremor was measured by the unified Parkinson's disease rating scale (UPDRS-Part III). A score of 4 on item 20 of the UPDRS was defined as a severe tremor. Disability was defined as interference of tremor in at least 2 daily living activities.
- Pre- and post-procedure total UPDRS scores, scores on items 20 and 21, and PDQ-39 were compared using a paired *t*-test and were considered statistically significantly different for $p < 0.05$.

Study population issues:

- The mean disease duration was 5.4 ± 2.8 years (range 2 to 10).
- All patients were right handed, with tremor more prominent on the right side in 4 of the patients.

Other issues: Not reported.

Key efficacy and safety findings

Efficacy	Safety																																						
<p>Number of patients analysed: 7</p> <p>Total average time in the MRI: 250.7 minutes. Total sonication time: 161.4 minutes.</p> <p>Procedure success: 100% (7/7) Tremor was abolished immediately after the procedure in all patients. One patient experienced relief of lower extremity tremor and rigidity as well.</p> <p>Re-emergence of tremor: 43% (3/7) Re-emergence of short-lasting, mild tremor was reported in 3 patients, 1 week ($n = 1$), 1 month ($n = 1$), and half a year ($n = 1$) after the procedure.</p> <p>Tremor (mean scores \pm SD)</p> <table border="1" data-bbox="110 772 792 1031"> <thead> <tr> <th></th> <th>Baseline</th> <th>1 week</th> <th>p value</th> </tr> </thead> <tbody> <tr> <td>UPDRS</td> <td>37.4 \pm 12.2</td> <td>18.8 \pm 11.1</td> <td>0.007</td> </tr> <tr> <td>Item 20 of UPDRS (rest tremor in the treated side)</td> <td>2.7 \pm 1.1</td> <td>0.0 \pm 0.0</td> <td><0.001</td> </tr> <tr> <td>Item 21 of UPDRS (action tremor in the treated side)</td> <td>3.0 \pm 1.0</td> <td>0.0 \pm 0.0</td> <td><0.001</td> </tr> </tbody> </table> <p>These effects were sustained (mean follow-up 7.3 months)</p> <p>Quality of life (mean score \pm SD)</p> <table border="1" data-bbox="110 1136 623 1209"> <thead> <tr> <th></th> <th>Baseline</th> <th>1 week</th> <th>p value</th> </tr> </thead> <tbody> <tr> <td>PDQ39</td> <td>42.3 \pm 16.4</td> <td>21.6 \pm 10.8</td> <td>0.008</td> </tr> </tbody> </table> <p>These effects were sustained (mean follow-up 7.3 months)</p> <p>Mini-Mental State Test (mean score, maximum 30) The minimal state examination was 30 in all patients before and after the procedure.</p> <p>Disability The clinical assessment of the examiner and patients changed from severe disability to no functional disability immediately after the procedure and during follow-up.</p>		Baseline	1 week	p value	UPDRS	37.4 \pm 12.2	18.8 \pm 11.1	0.007	Item 20 of UPDRS (rest tremor in the treated side)	2.7 \pm 1.1	0.0 \pm 0.0	<0.001	Item 21 of UPDRS (action tremor in the treated side)	3.0 \pm 1.0	0.0 \pm 0.0	<0.001		Baseline	1 week	p value	PDQ39	42.3 \pm 16.4	21.6 \pm 10.8	0.008	<p>Adverse events during sonications, % of patients (n/N)</p> <table border="1" data-bbox="821 275 1507 485"> <tbody> <tr> <td>Headache</td> <td>43% (3/7)</td> </tr> <tr> <td>Dizziness</td> <td>29% (2/7)</td> </tr> <tr> <td>Vertigo</td> <td>57% (4/7)</td> </tr> <tr> <td>Lip paraesthesia</td> <td>14% (1/7) Resolved after target was repositioned 1mm anteriorly</td> </tr> </tbody> </table> <p>Adverse events that lasted after the procedure, % of patients (n/N)</p> <table border="1" data-bbox="821 548 1507 709"> <tbody> <tr> <td>Hypogeusia</td> <td>14% (1/7)</td> </tr> <tr> <td>Subjective unsteady feeling when walking</td> <td>14% (1/7) Resolved</td> </tr> <tr> <td>Disturbance when walking tandem</td> <td>14% (1/7) Resolved at 2-month follow-up</td> </tr> </tbody> </table>	Headache	43% (3/7)	Dizziness	29% (2/7)	Vertigo	57% (4/7)	Lip paraesthesia	14% (1/7) Resolved after target was repositioned 1mm anteriorly	Hypogeusia	14% (1/7)	Subjective unsteady feeling when walking	14% (1/7) Resolved	Disturbance when walking tandem	14% (1/7) Resolved at 2-month follow-up
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<p>Abbreviations used: PD, Parkinson's disease; PDQ, Parkinson's disease questionnaire; SD, standard deviation; UPDRS, Unified Parkinson Disease Rating Scale.</p>																																							

Study 3 Zaaroor M (2017)

Details

Study type	Case series
Country	Israel
Recruitment period	2013-16
Study population and number	n= 30 patients including 9 with PD, 3 with ET-PD and 18 with ET
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. <u>Inclusion criteria:</u> patients with severe refractory tremor. <u>Exclusion criteria:</u> 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 PD and 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 PD and 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).
- Five patients had levodopa, 4 with PD and 1 with ET-PD. Patients with PD on levodopa suffered from motor fluctuations, whereas the patient with ET-PD did not.

Key efficacy and safety findings

Efficacy							Safety				
Number of patients analysed: 30 patients including 9 with PD , 3 with ET-PD and 18 with ET							Adverse Event	No. of Patients	Time to Resolution		
Tremor							Related to sonication				
	Patients with PD (n=9)				Patients with ET-PD (n=3)			Vertigo	47% (14/30)	Seconds	
	Baseline	After 1 month	After 6 months		Baseline	After 1 month	After 6 months	Headache	37% (11/30)	Seconds to minutes	
UPDRS Motor score (mean±SD)	24.9 ± 8.0	16.4 ± 11.1*	13.4 ± 9.2**		34.7 ± 7.1	22.7 ± 7.5	17.1 ± 7.1	Dizziness	13% (4/30)	Seconds to minutes	
Item 20 of the UPDRS	2.90 ± 0.99	0.40 ± 0.97***	0.3 ± 0.5***		-	-	-	Nausea	10% (3/30)	Minutes	
Item 21 of the UPDRS	3.00 ± 1.16	0.60 ± 0.97***	0.6 ± 1.1***		-	-	-	Burning scalp sensation	10% (3/30)	Seconds	
*p=0.042 for the comparison to baseline.									Vomiting	7% (2/30)	Minutes
** p=0.009 for the comparison to baseline.									Lip paraesthesia	7% (2/30)	Seconds
***p < 0.001 for the comparison to baseline.									Related to thalamotomy		
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.									Gait ataxia	17% (5/30) (3 ET, 1 PD, and 1 ET-PD)	1–3 months
Tremor recurrence during the first 6 months after the procedure (mean 2.5 months)									Unsteady feeling	13% (4/30)	1–4 weeks
Patients with PD: 22% (2/9)									Taste disturbance	13% (4/30)	1–3 months
Patients with ET-PD: 67% (2/3)									Asthenia	13% (4/30)	1–4 weeks
The tremor that recurred was significantly less disabling than before the procedure in all but 1 patient with ET-PD.									Hand ataxia	10% (3/30) (2 ET, 1 ET-PD)	1–4 weeks
Quality of life									Related to stereotactic frame		
	Patients with PD (n=9)				Patients with ET-PD (n=2)			Scalp numbness	17% (5/30)	1–4 weeks	
	Baseline	After 1 month	After 6 months		Baseline	After 1 month	After 6 months	Haematoma near the eye	10% (3/30)	1–2 weeks	
PDQ-39 Score (mean±SD)	38.6 ± 16.8	26.1 ± 7.2 ^a	20.6 ± 8.8 ^b		24	7	14				
					25	6	1				
^a p=0.036 for the comparison to baseline.											
^b p=0.008 for the comparison to baseline.											
The improvement in quality of life was sustained in 78% of the patients with PD, and 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.											
Abbreviations used: DBS, deep brain stimulation; ET, essential tremor; MRgFUS, MRI-guided focused ultrasound ;PD, Parkinson's disease; PDQ-39 = PD Questionnaire; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale; VIM, ventral intermediate nucleus.											

Study 4 Fasano A (2017)

Details

Study type	Case series
Country	Canada
Recruitment period	Not reported
Study population and number	n= 6 patients with tremor including 3 with PD , 2 with dystonic tremor in the context of cervicobrachial dystonia and writer's cramp, and 1 with dystonia gene-associated tremor
Age and sex	Mean 68 years; 83% (5/6) male
Patient selection criteria	Patients with tremors other than ET.
Technique	MRgFUS targeting the patient's dominant hemisphere.
Follow-up	6 months
Conflict of interest/source of funding	One of the authors is a consultant to the Focused Ultrasound Foundation and has received research support from InSightec in the past.

Analysis

Follow-up issues: One of the patients with PD died 4 months after surgery of the complication of pneumonia so the 6-month data refer to 5 patients.

Study design issues:

- All patients were videotaped with their head covered (to guarantee blinding).
- The primary endpoint was the reduction of lateralised items of the Tremor Rating Scale of contralateral hemibody assessed by a blinded rater.

Key efficacy and safety findings

Efficacy	Safety																
<p>Number of patients analysed: 6 patients with tremor including 3 with PD</p> <p>Tremor All patients achieved a statistically significant, immediate, and sustained improvement of the contralateral tremor score by 42%, 52%, 56%, and 53% at 1 week and 1, 3, and 6 months after the procedure, respectively (p<0.05). Mean composite score of lateralised items of TRS-A and -B was 17.0±2.7 at baseline.</p> <p>UPDRS (patients with PD only) Activities of daily living Baseline: 17.0±3.0 Latest follow-up: 11.5±2.5 p value not statistically significant</p> <p>Motor section Baseline: 27±1 Latest follow-up: 26.5±4.5 p value not statistically significant</p>	<p>All patients experienced transient side effects and 2 patients experienced persistent side effects at the time of last evaluation: hemitongue numbness and hemiparesis with hemihypoesthesia.</p> <p>One of the patients with PD experienced a decay of tremor benefit.</p> <p>Adverse events in patients with PD</p> <table border="1"> <thead> <tr> <th>Adverse event</th> <th>Number of patients with PD (n=3)</th> </tr> </thead> <tbody> <tr> <td>Local pain or burning</td> <td>2/3</td> </tr> <tr> <td>Dizziness</td> <td>1/3</td> </tr> <tr> <td>Numbness or paraesthesia</td> <td>1/3 (persistent)</td> </tr> <tr> <td>Headache</td> <td>1/3</td> </tr> <tr> <td>Dysarthria</td> <td>1/3</td> </tr> <tr> <td>Hemiparesis</td> <td>1/3 (persistent)</td> </tr> <tr> <td>Eyelid weakness</td> <td>1/3</td> </tr> </tbody> </table>	Adverse event	Number of patients with PD (n=3)	Local pain or burning	2/3	Dizziness	1/3	Numbness or paraesthesia	1/3 (persistent)	Headache	1/3	Dysarthria	1/3	Hemiparesis	1/3 (persistent)	Eyelid weakness	1/3
Adverse event	Number of patients with PD (n=3)																
Local pain or burning	2/3																
Dizziness	1/3																
Numbness or paraesthesia	1/3 (persistent)																
Headache	1/3																
Dysarthria	1/3																
Hemiparesis	1/3 (persistent)																
Eyelid weakness	1/3																
Abbreviations used: ET, essential tremor; MRgFUS, MRI-guided focused ultrasound; PD, Parkinson's disease; TRS, tremor rating scale; UPDRS, Unified Parkinson's Disease Rating Scale.																	

Study 5 Bond A E (2017)

Details

Study type	RCT with double-blinded assessments through the 3-month primary end point analysis
Country	USA (2 centres)
Recruitment period	2012-15
Study population and number	n= 27 (20 FUS thalamotomy versus 7 sham) patients with medication-refractory, tremor-dominant Parkinson Disease
Age and sex	Median 68 years; 96% (26/27) male
Patient selection criteria	Adult patients with idiopathic tremor-dominant Parkinson's Disease with a medication-refractory, severe and disabling disease.
Technique	MR-guided FUS thalamotomy. Sham treatment: the sonication power was set to zero watts.
Follow-up	1 year
Conflict of interest/source of funding	No conflict of interest was reported. The study was supported by the Focused Ultrasound Foundation, the Commonwealth of Virginia, Diane and David Heller, Robert and Mollie Hardie and the Prince Charitable Trust.

Analysis

Follow-up issues:

- Patients were clinically assessed at baseline, 1, 3 and 12 months after the procedure. After the procedure, MRI was done at day 1, day 30 and 1 year.
- After the 3-month blinded phase, in the treatment group, 3 patients had DBS and 3 patients were lost to follow-up. In the sham group, 1 patient opted for DBS and 6 patients had open-label FUS thalamotomy, including 1 patient subsequently lost to follow-up. Therefore, 19 patients were assessed at 1 year.

Study design issues:

- The study was intended to be a pilot study. Therefore, a formal power analysis was not done before initiating the study. A sample size of 30 was initially planned.
- 53 patients were first assessed for eligibility and 26 were deemed ineligible most commonly because of patient withdrawal (31%, 8/26) and failure to prove medication-refractory status (31%, 8/26).
- Patients assigned to a sham procedure were offered open-label treatment after the 3-month blinded assessment.
- Computer randomisation was done by the study coordinator and stored electronically. All patients were prepared identically with scalp shave, stereotactic frame placement, MRI and stereotactic planning. Before the initiation of sonications, the treatment team was informed of the randomisation assignment by the study coordinator. The patient and evaluators remained blinded to the assignment until after the 3-month assessment.
- The predefined primary outcomes were safety and difference in improvement between groups at 3 months in the on-medication treated hand tremor subscore from the CRST.
- The secondary outcomes were descriptive results of UPDRS scores and quality of life measures.
- Follow-up assessments were blinded at 1 and 3 months and unblinded at 1 year. The assessments were timed 1 hour after administration of the patients; morning dose of PD medications after at least 12 hours without medication.

Study population issues: Baseline characteristics between the treatment and sham groups were not statistically significantly different.

Other issues: Medication dose was not fixed during the trial, potentially confounding the results.

Key efficacy and safety findings

Efficacy			Safety		
Number of patients analysed: 27 (20 FUS thalamotomy versus 7 sham)			Adverse events		
CRST improvement from baseline to 3 months (median, IQR)					
	FUS thalamotomy	Sham procedure	FUS thalamotomy (n=20)	Sham procedure (n=7)	
Tremor subscore (CRST A+B), treated hand	7 (3.5 to 14.0) Baseline: 17 points	2 (3.0 to 6.0) Baseline: 23 points	Thalamotomy-related		
Tremor subscore (CRST A+B), treated hand, %	62 (22.0 to 79.0)	22 (-11.0 to 29.0)	Finger paraesthesia (transient)^a	35% (7/20)	NA
Total CRST	18 (12.0 to 25.0)	3 (-4.0 to 17.0)	Finger paraesthesia (persistent)^b	5% (1/20)	NA
Total CRST, %	44 (23.0 to 78.0)	12 (-8.0 to 37.0)	Orofacial paraesthesia (transient)	5% (1/20)	NA
Statistically significant between-group difference for the tremor subscore improvement (p=0.04).			Orofacial paraesthesia (persistent)	20% (4/20)	NA
UPDRS scores improvement from baseline to 3 months (median, IQR)			Ataxia (transient)	40% (4/20) ^c	NA
	FUS thalamotomy	Sham procedure	Ataxia (persistent)	5% (1/20)	NA
Resting tremor (item 20), treated hand	1.5 (0 to 3.0)	0 (0 to 0)	Hemiparesis (transient)	10% (2/20)	NA
Postural or action tremor (item 21), treated hand	1 (0.5 to 2.5)	0 (0 to 2.0)	Hemiparesis (persistent)	10% (2/20) ^d	NA
Motor (part III) subsection	8 (0.5 to 11.0) Baseline score: 23 points	1 (-5.0 to 9.0) Baseline score: 25 points	Dysmetria (transient)	5% (1/20)	NA
Total UPDRS	14 (6.5 to 16.0)	3 (-3.0 to 13.0)	Mild vocal change (persistent)	5% (1/20)	NA
Quality of life improvement from baseline to 3 months (median, IQR)			MRI or ultrasonography-related (all transient)		
	FUS thalamotomy	Sham procedure	Scalp numbness	5% (1/20)	0
PDQ-39 score	5.4 (-2.4 to 11.9)	7.6 (0.9 to 13.0)	Headache	60% (12/20)	43% (3/7)
CRST disability (part C) score	7.5 (1.0 to 12.5)	3 (0. to 4.0)	Dizziness or vertigo	40% (8/20)	14% (1/7)
Neuropsychological improvement from baseline to 3 months (median, IQR)			Head pain or heat sensation	15% (3/20)	0
	FUS thalamotomy	Sham procedure	Stomach pain or nausea or emesis	20% (4/20)	14% (1/7)
MoCA score*	0 (-1.5 to 2.5)	1 (-1.0 to 2.0)	Periorbital swelling	10% (2/20)	0
BDI-II score**	0 (-3.0 to 2.0)	1 (-2.0 to 2.0)	Neck or back or shoulder pain	20% (4/20)	14% (1/7)
LEDD, mg	0 (0 to 150)	0 (-200 to 0)	Decline in mental status	5% (1/20)	0
* Scores for the MoCA range from 0 to 30, with lower scores indicating impairment.			Pin site pain	5% (1/20)	28% (2/7)
**Scores for the BDI-II range from 0 to 63, with higher scores indicating more depressive symptoms.			Anxiety	5% (1/20)	0
			Light headedness	10% (2/20)	0
			Right-sided ecchymosis	5% (1/20)	0
			Spot in visual field	5% (1/20)	0
			Unrelated		

	Decline in visuospatial abilities	5% (1/20)	0
	Brief loss of reality	5% (1/20)	0
	Increased daytime sleepiness	5% (1/20)	0
	Decreased hand dexterity	10% (2/20)	0
	Worsening degenerative knee disease	5% (1/20) ^e	0
	Cholecystitis or cholecystectomy	5% (1/20) ^e	0
	Worsening of depression	5% (1/20) ^e	0
	^a Transient was defined as resolved during the 1-year study. ^b Persistent was defined as still present at the last follow-up. ^c One patient reported as a serious adverse event. ^d Reported as a serious adverse event. ^e From the procedure environment. There were no statistically significant differences in the adverse events between the blinded thalamotomy and the blinded sham procedure groups.		
Abbreviations used: BDI-II, Beck depression inventory; CRST, clinical rating scale for tremor; DBS, deep brain stimulation; FUS, focused ultrasound; IQR, interquartile range; LEDD, levodopa-equivalent daily dosage; MoCA, Montreal cognitive assessment; NA, not applicable; PD, Parkinson's disease; PDQ-39 = PD Questionnaire; UPDRS, Unified Parkinson's Disease Rating Scale.			

Validity and generalisability of the studies

- One RCT was included in table 2.⁵
- The 4 case series included in table 2 only included 13, 7, 12 and 3 patients, and had a maximum mean follow-up of 11.5 months.¹⁻⁴

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 treatment-resistant essential tremor. NICE interventional procedure guidance XXX (2017). Available from <http://www.nice.org.uk/guidance/IPGXXX>
- Magnetic resonance image-guided transcuteaneous focused ultrasound for uterine fibroids. NICE interventional procedure guidance 413 (2011). Available from <http://www.nice.org.uk/guidance/IPG413>
- Subthalamotomy for Parkinson's disease. NICE interventional procedure guidance 65 (2004). Available from <http://www.nice.org.uk/guidance/IPG65>
- Deep brain stimulation for Parkinson's disease. NICE interventional procedure guidance 19 (2003). Available from <http://www.nice.org.uk/guidance/IPG19>

NICE guidelines

- Parkinson's disease in over 20s: diagnosis and management. NICE guideline 35 (2006) Available from <http://www.nice.org.uk/guidance/cg35>

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

IP overview: unilateral MRI-guided focused ultrasound thalamotomy for moderate to severe tremor in Parkinson's disease

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 moderate to severe tremor in Parkinson's disease 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 Study to Evaluate Safety and Initial Effectiveness of ExAblate Transcranial MR Guided Focused Ultrasound for Unilateral Thalamotomy in the Treatment of Medication-Refractory Tremor Dominant Idiopathic Parkinson's Disease](#). NCT01772693. RCT; USA; Enrolment: 27; estimated completion date: September 2017.
 - [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.
 - [ExAblate Transcranial MRgFUS of the Globus Pallidum for Treatment of Parkinson's Disease](#) NCT02263885. Case series; USA; Enrolment: 20; estimated completion date: December 2017.

- [ExAblate Transcranial MRgFUS of the Subthalamic Nucleus for Treatment of Parkinson's Disease](#) NCT02246374. Case series; USA; Enrolment: 10; estimated completion date: October 2017.
 - [ExAblate Transcranial MRgFUS for Unilateral Pallidotomy for the Treatment of Parkinson's Disease](#) NCT02347254. Case series; Canada; Enrolment: 6; estimated completion date: December 2017.
 - [A Feasibility Study to Evaluate Safety and Initial Effectiveness of ExAblate Transcranial MR Guided Focused Ultrasound for Unilateral Pallidotomy in the Treatment of Dyskinesia of Parkinson's Disease](#) NCT02003248. Case series; Republic of Korea; Enrolment: 5; estimated completion date: May 2017.
- Some patients may not be able to have MRI.

References

1. Magara A, Buhler R, Moser D et al. (2014) First experience with MR-guided focused ultrasound in the treatment of Parkinson's disease. *Journal of Therapeutic Ultrasound* 2, 11
2. Schlesinger I, Eran A, Sinai A et al. (2015) MRI Guided Focused Ultrasound Thalamotomy for Moderate-to-Severe Tremor in Parkinson's Disease. *Parkinsons Disease* 2015, 219149
3. 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
4. Fasano A, Llinas M, Munhoz RP et al. (2017) MRI-guided focused ultrasound thalamotomy in non-ET tremor syndromes. *Neurology* 89(8), 771-775
5. Bond AE, Shah BB, Huss DS et al. (2017) Safety and Efficacy of Focused Ultrasound Thalamotomy for Patients With Medication-Refractory, Tremor-Dominant Parkinson Disease. A Randomized Clinical Trial. *JAMA Neurol*. Published online October 30, 2017. doi:10.1001/jamaneurol.2017.3098

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
Schlesinger I, Sinai A, and Zaaroor M (2017) MRI-Guided Focused Ultrasound in Parkinson's Disease: A Review. <i>Parkinsons Disease</i> 2017, 8124624	Review n=3 studies	MRgFUS is a new option for PD patients with medication resistant symptoms. It is approved for this indication in Israel, Europe, Korea, and Russia. Further studies are needed in order to better characterise patient selection and treatment targets.	2 of the studies included in the review were already included in Table 2. The third one was retrieved after the post-consultation literature search (Zaaroor 2017) and was suggested for inclusion in Table 2.
Rohani M, and Fasano A (2017) Focused Ultrasound for Essential Tremor: Review of the Evidence and Discussion of Current Hurdles. <i>Tremor and Other Hyperkinetic Movements</i> 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.

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane)	24/10/2017	Issue 10 of 12, October 2017
Cochrane Central Database of Controlled Trials - CENTRAL	24/10/2017	Issue 9 of 12, September 2017
HTA database (Cochrane)	24/10/2017	Issue 4 of 4, October 2016
MEDLINE (Ovid)	24/10/2017	1946 to October Week 2 2017
MEDLINE In-Process (Ovid)	24/10/2017	October 23, 2017
EMBASE (Ovid)	24/10/2017	1974 to 2017 Week 43
PubMed	24/10/2017	n/a
JournalTOCS [for update searches only]	24/10/2017	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 thalamotom*.tw.
- 31 30 and 10
- 32 29 or 31
- 33 (MRgFUS or MRgHIFU).tw.
- 34 32 or 33
- 35 exablate.tw.

36 34 or 35

37 animals/ not humans/

38 36 not 37

39 (201703* or 201704* or 201705* or 201706* or 201707* or 201708* or 201709* or 20171*).ed.

40 38 and 39