

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of transcranial MRI-guided focused ultrasound thalamotomy for neuropathic pain

Neuropathic pain (nerve pain) can happen when damage to nerves affects pain signals to the brain. In this procedure, the patient lies inside an MRI scanner with a frame attached to their shaved head, and chilled water is circulated around the outside of the head to keep it cool. Focused ultrasound is then delivered to a small part of the brain responsible for transmitting pain signals (the thalamus) to destroy it. The procedure takes about 3 hours. The aim of the procedure is to relieve the pain.

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Introduction

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

Date prepared

This overview was prepared in April 2018 and updated in September 2018.

Procedure name

- Transcranial MRI-guided focused ultrasound thalamotomy for neuropathic pain.

Specialist societies

- British Society of Neuroradiologists
- Society of British Neurological Surgeons
- Association of British Neurologists
- British Pain Society
- Royal College of Anaesthetists – Faculty of Pain Medicine.

Description of the procedure

Indications and current treatment

Neuropathic pain results from dysfunction of sensory nerves and pathways in the nervous system. It can occur in a heterogeneous group of disorders, including painful diabetic neuropathy, post-herpetic neuralgia and trigeminal neuralgia. People with neuropathic pain may have altered pain sensation, areas of numbness or burning, and continuous or intermittent evoked or spontaneous pain. Neuropathic pain is an unpleasant sensory and emotional experience that can have a significant effect on a person's quality of life.

A range of different drugs are used to manage neuropathic pain, including antidepressants, anti-epileptic drugs, opioids, and topical treatments such as IP overview: Transcranial MRI-guided focused ultrasound thalamotomy for neuropathic pain

capsaicin and lidocaine (see NICE's guideline on [neuropathic pain: the pharmacological management of neuropathic pain in adults in non-specialist settings](#)). Neuropathic pain is often difficult to treat, because it can be refractory to many medications and because of the adverse effects associated with some drug treatments.

For neuropathic pain that is refractory to drug treatment, other options include percutaneous electrical nerve stimulation, spinal cord stimulation and deep brain stimulation.

What the procedure involves

Transcranial MRI-guided focused ultrasound thalamotomy for neuropathic pain is done with the patient lying supine inside an MRI scanner. The patient's head is shaved and a stereotactic head frame is attached. Patients are awake so they can report any improvement or adverse events to the operator during the procedure. However, they may be offered light sedation. Continuous MRI and thermal mapping are used to identify the target area of the brain and monitor treatment. Low-power ultrasound is delivered to confirm the chosen location. Then, high-power focused ultrasound pulses are administered to irreversibly ablate the 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 pain relief should occur within a day of the procedure.

Efficacy summary

Procedural success

In a case series of 11 patients, the procedure was considered to be complete in 9 patients; in 2 patients, 48 hours after the procedure, the therapeutic lesions were too small to sufficiently cover the target area.¹

Pain relief

In the case series of 11 patients, the overall mean pain relief was 57% at 1-year follow-up (n=8). The mean visual analogue scale score for pain was 59.5 before the procedure and 35.3 at 1-year follow-up (n=8). Of the 8 patients who had a complete procedure and had 1 year follow-up data, 5 took no drugs for pain and 3 maintained a globally unchanged regimen.¹

Quantitative electroencephalogram assessment

In the case series of 11 patients, electroencephalogram showed that spectral power was elevated in all frequency bands (delta-beta) at baseline. At 3- and

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12-month follow-up, frequency-band specific spectral power amplitudes were reduced in the 8 patients with available data, and were approaching the spectral curve seen in healthy volunteers.¹

Precision of transcranial MRI-guided focused ultrasound targeting

In the case series of 11 patients, lesion reconstructions (18 lesions in 9 patients) showed targeting precision within a millimetre for all 3 coordinates (dorsorostral, anteroposterior and mediolateral).¹

Safety summary

Bleeding

A bleed was reported in 1 patient in the case series of 11 patients. In the last minutes of the procedure, the patient had the acute appearance of right-sided motor hemineglect with dysmetria of the arm and leg, and dysarthria. MRI immediately and 48 hours later showed a bleed 8 mm to 10 mm in maximal diameter centred in the targeted posterior part of the thalamic central lateral nucleus, as well as ischaemic changes in the posterior part of the thalamic motor ventral lateral nucleus. Subsequent MRI showed good progressive resorption of the bleeding. Clinically, there was a 70% to 80% reduction in the motor symptoms over the next 24 hours. Over time, all dysmetric manifestations disappeared except during activation of the finer functions of speaking and writing, which remained impaired during demanding and stressful personal and professional interactions at 1-year follow-up.¹

Paraesthesia

Paraesthesia during the procedure was reported in 4 out of 11 patients in the case series of 11 patients.¹

Dysaesthesia

Dysaesthesia or pain was reported in 9 out of 11 patients in the case series of 11 patients.¹

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, specialist advisers did not

describe any anecdotal adverse events. They considered that the following were theoretical adverse events: hemiparesis and postoperative temporary local oedema causing minor transient thalamic symptoms.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to transcranial MRI-guided focused ultrasound thalamotomy for neuropathic pain. The following databases were searched, covering the period from their start to 25 July 2018: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched. No language restriction was applied to the searches (see [literature search strategy](#) for details). 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 neuropathic pain.
Intervention/test	Transcranial 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 52 patients who had transcranial MRI-guided focused ultrasound thalamotomy for neuropathic pain from 3 case series.¹⁻³ One of the case series is described in a review from the same study centre as an earlier case series; it provides limited safety and efficacy data on 18 patients, and is likely to include the previous 11 patients.²

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

Table 2 Summary of key efficacy and safety findings on transcranial MRI-guided focused ultrasound thalamotomy for neuropathic pain

Study 1 Jeanmonod D (2012)

Details

Study type	Case series
Country	Switzerland
Recruitment period	Not reported
Study population and number	n=11 (1 additional patient was enrolled but did not have the procedure) Patients with chronic therapy-resistant neuropathic pain.
Age and sex	Age range 45 to 75 years; sex not reported
Patient selection criteria	Patients with chronic therapy-resistant neuropathic pain.
Technique	Device: ExAblate 4000 (InSightec). The target area was the posterior part of the thalamic central lateral nucleus. Typically, sonifications of 10 to 20 seconds in duration were applied with up to a maximum acoustic power of 1200 and 800 W respectively, corresponding to 12,000 J per sonication. The mean peak focal temperature achieved in the treatments was 53±3.3°C (range 48° to 61°C). Two patients needed a subcutaneous opiate injection for back pain because of the extended time in a motionless supine position on the MRI table. The central lateral thalamotomy was done unilaterally (contralateral to the pain location) in 5 patients and bilaterally in 6 patients. The reasons for a unilateral procedure were: as a complement to radiofrequency treatment (n=2), and for bleeding (n=1), immediate pain relief after treatment of first side (n=1) and intolerance of longer intervention time (n=1). Improvements were made to the procedure during the study to increase the targeting accuracy.
Follow-up	1 year
Conflict of interest/source of funding	One of the authors is an employee of InSightec.

Analysis

Follow-up issues: At 1 year, results were available for 73% (8/11) of patients who had the procedure: 2 patients were lost to follow-up and 1 patient died from an unrelated medical cause. For safety reasons, the first patient who was enrolled in the study had a thermal spot of only 42°C, which did not result in a thermolesion and the patient was excluded from further analysis.

Study design issues: Small, prospective case series. Pain was assessed before and after the procedure using a detailed questionnaire, including the items of the McGill Pain Questionnaire. A visual analogue scale rating was used to assess pain intensity from 0 (least pain) to 100 (worst pain). In addition, patients provided a global percentage value of postoperative pain relief as compared with the preoperative state. Patients were assessed by clinical examination 24 and 48 hours after the procedure, telephone consultation at 1-month follow-up, and full reassessment at 3 months and 1 year after treatment. Eight patients had an electroencephalogram at 3- and 12-month follow-up.

Study population issues: Of the 12 patients initially enrolled in the study, 3 had facial pain, 1 had thoracic pain, 3 had lower extremity pain, 4 had upper extremity pain and 1 patient had hemibody pain. The duration of pain before the procedure ranged from 1.5 to 21.0 years (mean 8.5 years). Four patients had previously had treatment with radiofrequency central lateral thalamotomy. It is likely that these patients were also included in the cohort of patients reported in study 2 (Bauer et al., 2014).

Key efficacy and safety findings

Efficacy					Safety																																																																	
Number of patients analysed: 11					During the procedure, patients reported vestibular effects with or without vegetative manifestations (n=8), paraesthesia (n=4), dysaesthesia or pain (n=9).																																																																	
In the first 2 patients, the therapeutic lesions as seen 48 hours after the procedure were too small to sufficiently cover the target area. The procedure, therefore, was only considered complete in 9 of the 11 patients.					Displacement of the headframe occurred in 1 patient; it was repositioned without negative consequences.																																																																	
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IP overview: Transcranial MRI-guided focused ultrasound thalamotomy for neuropathic pain

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Precision of transcranial MRI-guided focused ultrasound targeting (differences between centres of the sonication lesions and presurgical target coordinates, mm); n=9 patients, 18 lesions

	Total patients		First group		Second group	
	mean±sd	median	mean±sd	median	mean±sd	median
No. of patients	9		5		4	
Dorsoventral	0.58±0.63	0.5	0.61±0.57	0.5	0.56±0.68	0
Anteroposterior	0.78±0.65	1.0	1.17±0.58	1.5	0.39±0.46	0
mediolateral	0.83±0.78	0.5	1.01±0.85	0.7	0.82±0.79	0.5

The thermolesions as seen on MRI 2 days after sonication were surrounded by a vasogenic oedema, which was no longer visible after 1 month. Visualisation of the lesion itself receded between 1 and 3 months.

Quantitative electroencephalogram assessment (n=8)

At baseline, spectral power was elevated in all frequency bands (delta-beta). At 3- and 12-month follow-up, frequency-band specific spectral power amplitudes were reduced, and were approaching the spectral curve of healthy volunteers.

Abbreviations used: sd, standard deviation

Study 2 Bauer R (2014)

Details

Study type	Case series
Country	Switzerland
Recruitment period	Not reported
Study population and number	n=18 Patients with neuropathic pain.
Age and sex	Not reported
Patient selection criteria	Not reported
Technique	Device: ExAblate Neuro focused ultrasound system (InSightec).
Follow-up	1 year
Conflict of interest/source of funding	None

Analysis

Follow-up issues: The paper states that more than 60 patients with neuropathic pain have had treatment to date. Results at 1-year follow-up are given for a cohort of 18 patients. There are no details about completeness of follow-up.

Study design issues: The publication is a review with limited information on safety and efficacy outcomes for a small cohort of patients.

Study population issues: This cohort is likely to have included the patients reported in study 1 (Jeanmonod D et al., 2012).

Key efficacy and safety findings

Efficacy	Safety
<p>Number of patients analysed: 18</p> <p>The paper notes that more than 60 patients with neuropathic pain have had treatment to date.</p> <p>The average pain relief in a cohort of 18 patients at 1-year follow-up was between 48% and 57%, measured on a visual analogue scale. Pain relief ranged from no effect to complete absence of pain.</p>	<p>There was 1 serious adverse effect: a transient hemineglect with dysarthria after a cavitation-induced haemorrhage. The patient needed neuro-rehabilitation.</p>

Study 3 Gallay MN (2018)

Details

Study type	Case series
Country	Switzerland
Recruitment period	2011 to 2016
Study population and number	n=136 (180 treatments); 41 patients had 46 treatment sessions for neuropathic pain. The remaining patients had Parkinson's disease (n=59), essential tremor (n=33) or cerebellar tremor (n=2). The indication was not stated for 1 patient who had an aborted treatment. Patients with chronic and therapy-resistant neuropathic pain, Parkinson's disease, essential tremor or cerebellar tremor.
Age and sex	Mean age: 66 years for all patients (62 years for patients with neuropathic pain); 29% female (all patients)
Patient selection criteria	Patients were seen by neurologists or pain specialists who confirmed the diagnosis and the resistance to drug treatment. No patient took anticoagulant or antiplatelet drugs within 10 days of the procedure. All patients had normal electrolyte and coagulation status.
Technique	The different surgical targets used were the pallidothalamic tract (n=105), the cerebellothalamic tract (n=50), the central lateral nucleus (n=84), the centrum medianum (n=12), and the globus pallidus (n=2). All procedures used the ExAblate Neuro device (InSightec). All 41 patients with neuropathic pain had a bilateral target.
Follow-up	1 year
Conflict of interest/source of funding	None

Analysis

Follow-up issues: 1 patient with essential tremor was lost to follow-up.

Study design issues: Prospective single-centre case series of consecutive treatments. The main aim of the study was to report side effects and targeting accuracy.

Study population issues: The mean symptom duration for patients with neuropathic pain was 16 years.

Other issues: The procedure was aborted in 2 patients: 1 patient with Parkinson's disease could not cope emotionally with the procedure, which had to be interrupted before ultrasound application and the other procedure had to be aborted because it was not possible to achieve therapeutic heat application in the target.

Key efficacy and safety findings

Efficacy	Safety
<p>Number of patients analysed: 134</p> <p>Cognitive status</p> <p><i>Mean MMSE score</i></p> <ul style="list-style-type: none"> Preoperative=29.0±1.2 (n=29) Postoperative (1 to 2 days after treatment)=29.5±0.8 (n=29), p=0.06 1 year follow-up=29.4±1.3 (n=25), p=0.2 <p><i>Mean MoCA score</i></p> <ul style="list-style-type: none"> Preoperative=27.1±2.7 (n=149) Postoperative (1 to 2 days after treatment)=28.1±2.1 (n=147), p=0.002 1 year follow-up=28.0±2.8 (n=82), p=0.02 <p>In 23 patients, the MoCA score improved by 3 points or more from the preoperative assessment at the assessment 2 days after the procedure. In 14 of these patients, the postoperative MoCA score was in the normal range (26 to 30). In 7 patients, there was a drop of 3 points or more at 2 days. In 2 of these patients, the final MoCA score was below 26 points.</p> <p>Targeting accuracy</p> <p>234 out of 253 thermal lesions could be reconstructed postoperatively.</p> <p><i>Mean accuracy (mm)</i></p> <ul style="list-style-type: none"> Mediolateral=0.32±0.29 Anteroposterior=0.29±0.28 Dorsoventral=0.44±0.39 <p>Mean 3D accuracy=0.73±0.39 mm</p>	<p>Procedure-related side effects</p> <ul style="list-style-type: none"> Benign subcutaneous facial swelling, n=2 (resolved within a week) Short episodes of right-sided frontal headache, n=1 (resolved spontaneously on day 2 after the procedure) Temporary unilateral blindness during frame fixation after induction of supraorbital local anaesthesia, n=1 (an aberrant extension of the lateral orbital fissure was retrospectively identified on CT scan; there was some small petechial bleeding on the retina, treated later by laser surgery, and the patient recovered his eyesight completely) <p>Head pain during procedure (scale 0 to 4)</p> <ul style="list-style-type: none"> Little or no pain (0 to 1) =48.3% Moderate (2) =14% Brief (less than 10 seconds) but strong pain (3 to 4)=37.6% <p>Effects on neighbouring structures</p> <ul style="list-style-type: none"> Slight hypaesthesia on lower lip and slight reduction of gustation, n=1 (absent at 3 month follow-up evaluation) Paraesthesia around the mouth and left hand, n=1 (fully resolved after a few weeks) Postoperative decompensation of mnemonic function in 1 patient with Parkinson's disease. <p>General side effects</p> <ul style="list-style-type: none"> Lung embolism 10 days after the procedure, n=1 Cardiac decompensation, n=1 (4 days after the procedure, in a patient with known heart disease) Bladder infection, n=1 (in a patient with a urinary catheter) Hiccups, n=1 (lasted 1 day on the first day after treatment) Broken elbow caused by a fall, n=1 <p>Disease related side effects</p> <ul style="list-style-type: none"> Suicide attempt, n=1 (2 months after an uneventful 1-sided treatment), while patient was hospitalised in a psychiatric environment. The patient had Parkinson's disease and had significant preoperative cognitive deficits (MoCA 22/30). Cognitive difficulties in a patient with advanced Parkinson's disease, n=1 (the patient had nearly recovered to preoperative baseline at 1 year follow-up). Severe fatigue and apathy, n=1 (patient had Parkinson's disease and was hospitalised in a rehabilitation centre for a few weeks. At 3 months' follow-up, he was living independently again). Increase in hypophonia, n=2. Mildly slurred speech 2 days after the procedure, n=2 (both patients had severe essential tremor with preoperative cerebellar deficits; in 1 patient, slurring was barely detectable at 3 months and in the other it was only detectable 2 days after the procedure by the family of the patient in his mother language but not in English). <p>There was no bleeding.</p>

Abbreviations used: MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment

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Validity and generalisability of the studies

- Only 2 small published case series were identified, which were both based in Switzerland.
- The treated neuropathic pain syndromes included various body parts (face, arm, leg, trunk and hemibody).
- The case series of 11 patients (study 1) represents the first experience of using transcranial MRI-guided focused ultrasound thalamotomy to treat neuropathic pain.
- In the case series of 11 patients, the procedure was modified during the study to improve targeting accuracy and this is likely to have affected the efficacy outcomes.
- After the last patient in the case series of 11 patients had treatment, 2 new safety measures were introduced to reduce the risk of bleeding.
- The maximum follow-up was 1 year.

Existing assessments of this procedure

A Health Technology Assessment from Sweden on 'Transcranial Magnetic Resonance Guided Focused Ultrasound Treatment of Essential Tremor, Neuropathic Pain and Parkinson's Disease' was published in October 2015.⁴ The report included 1 case series on neuropathic pain. It concluded:

'In patients with neuropathic pain or Parkinson's disease, pain and symptom scores were respectively improved in very small case series. The certainty of evidence was very low. Although the short term results are promising, the long term results including complications remain to be evaluated. The available case series can be considered as feasibility studies of a newly developed technology. The method has the advantage of being non-invasive. Severe complications are uncommon. The equipment is very expensive and requires large investments.'

Related NICE guidance

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

Interventional procedures

- Percutaneous electrical nerve stimulation for refractory neuropathic pain. NICE Interventional procedures guidance 450 (2013). Available from <http://www.nice.org.uk/guidance/IPG450>
- Deep brain stimulation for refractory chronic pain syndromes (excluding headache). NICE Interventional procedures guidance 382 (2011). Available from <http://www.nice.org.uk/guidance/IPG382>
- Unilateral MRI-guided focused ultrasound thalamotomy for moderate to severe tremor in Parkinson's disease. NICE Interventional procedures guidance 606 (2018). Available from <http://www.nice.org.uk/guidance/IPG606>

Technology appraisals

- Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin. NICE Technology appraisal guidance 159 (2008). Available from <http://www.nice.org.uk/guidance/TA159>

NICE guidelines

- Neuropathic pain in adults: pharmacological management in non-specialist settings. NICE Clinical Guideline 173 (2013). Available from <http://www.nice.org.uk/guidance/CG173>

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. Two Specialist Adviser Questionnaires for transcranial MRI-guided focused ultrasound thalamotomy for neuropathic pain were submitted and can be found on the [NICE website](#).

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Patient commentators' opinions

NICE's Public Involvement Programme will send questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). When NICE has received the completed questionnaires, these will be discussed by the committee.

Company engagement

A structured information request was sent to 1 company who manufactures 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

None other than those described above.

References

1. Jeanmonod D, Werner B, Morel A et al. (2012) Transcranial magnetic resonance imaging-guided focused ultrasound: noninvasive central lateral thalamotomy for chronic neuropathic pain. *Neurosurgical Focus* 32 (1): E1 doi:<https://doi.org/10.3171/2011.10.FOCUS11248>
2. Bauer R, Martin E, Haegele-Link S et al. (2014) Noninvasive functional neurosurgery using transcranial MR imaging-guided focused ultrasound. *Parkinsonism and related disorders* 20S1: S197–199
3. Gallay MN, Moser D and Jeanmonod D (2018) Safety and accuracy of incisionless transcranial MR-guided focused ultrasound functional neurosurgery: single-center experience with 253 targets in 180 treatments *Journal of neurosurgery*: 1-10
4. Corneliuson O, Björk-Eriksson T, Daxberg E-L, Fhager A, Persson J, Pettersson J, Sjögren P, Skagervik I, Strandell A. *Transcranial Magnetic Resonance Guided Focused Ultrasound for Treatment of Essential Tremor, Neuropathic Pain and Parkinson's Disease.* [Transkraniell magnetkamerakontrollerad fokuserad ultraljudsbehandling för essentiell tremor, neuropatisk smärta och Parkinsons sjukdom]. Göteborg: Västra Götalandsregionen, Sahlgrenska Universitetssjukhuset, HTA-centrum; 2015. *Regional activity-based HTA* 2015:82

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	25/07/18	Issue 7 of 12, July 2018
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	25/07/18	Issue 7 of 12, July 2018
HTA database (Cochrane Library)	25/07/18	-
MEDLINE (Ovid)	25/07/18	1946 to July 24, 2018
MEDLINE In-Process (Ovid) & Medline ePub ahead (Ovid)	25/07/18	July, 24 2018
EMBASE (Ovid)	25/07/18	1974 to 2018 Week 30
BLIC	25/07/18	-

Trial sources searched 31st January 2018

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

Websites searched on 31st January 2018

- 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	Magnetic Resonance Imaging/
2	MAGNETIC RESONANCE IMAGING, INTERVENTIONAL/
3	MRI.tw.
4	((MR or magnet*) adj4 (guid* or imag*)).tw.
5	(magnet* adj4 resonanc*).tw.

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6	High-Intensity Focused Ultrasound Ablation/
7	exp Ultrasonic Therapy/
8	(focus* adj4 (ultraso* or ultra-so*)).tw.
9	Ultrasonic Surgical Procedures/
10	(focus* adj4 acoustic* adj4 energy*).tw.
11	(ultrasonograph* adj4 intervention*).tw.
12	HIFU.tw.
13	(MRgFUS or MRgHIFU).tw.
14	or/1-13
15	THALAMUS/
16	(thalamus or thalamoto* or thermoablat* or thalamic or brain or brains or cranium*).tw.
17	(thermal* adj4 ablat*).tw.
18	or/15-17
19	Neuralgia/
20	((Neurogen* or Neuropathic* or nerve* or neuralgi*) adj4 pain).tw.
21	Peripheral Nervous System Diseases/
22	peripher* nervou* system diseas*.tw.
23	*Chronic pain/
24	or/19-23
25	14 and 18 and 24
26	exablate neuro.tw.
27	25 or 26
28	animals/ not humans/
29	27 not 28

Appendix

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

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non- inclusion in table 2
Martin E, Jeanmonod D, Morel A, et al. (2009) High-intensity focused ultrasound for noninvasive functional neurosurgery Annals of Neurology 66: 858-61	Case series n=9 Follow-up=48 hours	All treatments were well tolerated, without side effects or neurological deficits. This is the first report on successful clinical application of tcMRgHIFU in functional brain disorders, portraying it as safe and reliable for non-invasive neurosurgical interventions.	The same patients are included in study 1 (Jeanmonod D et al., 2012), which has a longer follow-up.