

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of 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.

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Introduction

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

Date prepared

This overview was prepared in March 2017.

Procedure name

- 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 MR 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 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

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 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 MRI-guided focused ultrasound thalamotomy, the mean \pm standard deviation 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 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

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

Quality of life

In the case series of 7 patients, the mean Parkinson's Disease Questionnaire-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

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

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

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

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

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

Taste disturbance

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

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

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 moderate to severe tremor in Parkinson's disease. 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	<p>Clinical studies were included. Emphasis was placed on identifying good quality studies.</p> <p>Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study.</p> <p>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.</p>
Patient	Patients with moderate to severe tremor in Parkinson's disease.
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 20 patients from 2 case series^{1,2}.

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 appendix A.

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Table 2 Summary of key efficacy and safety findings on 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	<u>Inclusion criteria:</u> 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) MR imaging 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 received 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 MR 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 thermoagulations 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>Inclusion criteria: 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>Exclusion criteria: 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 Parkinson's disease questionnaire (PDQ39) 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 following 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 716"> <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>																																							

Validity and generalisability of the studies

- No randomised controlled trial was included in table 2.
- The 2 case series included in table 2 only included 13 and 7 patients, and had a maximum mean follow-up of 7 months.^{1,2}

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 treatment-resistant essential tremor. NICE interventional procedure guidance XXX (2017). Available from
- Magnetic resonance image-guided transcatheter 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 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 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 Anouk, Buhler Robert, Moser David 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 Ilana, Eran Ayelet, Sinai Alon et al. (2015) MRI Guided Focused Ultrasound Thalamotomy for Moderate-to-Severe Tremor in Parkinson's Disease. *Parkinsons Disease* 2015, 219149

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Additional relevant papers

There were no additional papers identified.

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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/

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