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Transcranial Magnetic Resonance Guided Focused Ultrasound Treatment of Essential Tremor, Neuropathic Pain and Parkinson's Disease

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Sjögren P, Skagervik I, Strandell A

Transcranial Magnetic Resonance Guided Focused Ultrasound Treatment of Essential Tremor, Neuropathic Pain and Parkinson's Disease.[Transkraniell magnetkamerakontrollerad fokuserad ultraljudsbehandling för essentiell tremor, neuropatisk smärta och Parkinsons sjukdom]

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1. Abstract

Background

Magnetic Resonance Guided Focused Ultrasound (MRgFUS) is a novel technique in which ultrasound waves are stereotactically focused into deep structures in the brain, to increase the temperature to an ablational level. The process is monitored in real-time by magnetic resonance (MR) thermometry. Extracranially, the technique is currently used for the treatment of uterine fibroids and alleviation of pain from bone metastases. Transcranial (tcMRgFUS) application is of recent date, mostly within the field of functional neurosurgery. Patients refractory to first-line treatment are currently treated with invasive deep brain stimulation (DBS).

Objective To evaluate the effect of tcMRgFUS in patients with essential tremor, neuropathic pain or Parkinson's disease, compared with DBS or the natural course of the disorder.

Methods

A systematic literature search was conducted in PubMed, Embase, the Cochrane Library, and a number of HTA-databases. At least two persons independently screened titles, abstracts and full-text articles for inclusion and extracted data. The certainty of evidence was rated according to the GRADE system.

Main results

The search resulted in five published case series. All analyses were based on intra-individual comparisons before and up to one year after treatment. The results were also evaluated against the natural course. Randomised trials are on-going.

Essential tremor was studied in three small case series. Health related quality of life (HRQoL) was improved, measured as a 70% reduction in Essential Tremor Questionnaire scores, very low certainty of evidence (GRADE ⊕○○○). Activity of Daily Living (ADL) was improved, measured as a 51-80 % reduction in Clinical Rating of Score for Tremor (CRST) for disability, very low certainty of evidence (GRADE ⊕○○○). Symptom score was improved, measured as a 39-85 % reduction in CRST for hand tremor, which is considered as an important improvement for the patient. Very low certainty of evidence (GRADE ⊕○○○).

Neuropathic pain was studied in one small case series. Pain score was improved, measured as a 41 % reduction in VAS, very low certainty of evidence (GRADE ⊕○○○).

Parkinson's disease was studied in one small case series. Symptom score was improved, measured as a 61 % reduction in Unified Parkinson Disease Rating Scale (UPDRS), very low certainty of evidence (GRADE ⊕○○○).

Ethical aspects:


The non-invasive technique is likely to cause less complications than DBS. Its non-invasive nature may open up for larger patient groups that are currently not considered for DBS. The high investment costs are likely to cause displacement effects.

Economical aspects:

The initial investment costs are very high; 14 million SEK for the MRgFUS equipment and 20-25 million SEK for a MRI scanner.

Concluding remarks

In patients with essential tremor, the effect of tcMRgFUS on symptom score for tremor was immediate. The effect on symptom score, ADL and HRQoL was large and remained when measured up to one year after the procedure. Contrary, the natural course implies progressive deterioration. 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.

2. Svensk sammanfattning – Swedish summary

Bakgrund

Transkraniell MRgFUS är en tekniskt avancerad teknologi. Med hjälp av MR fokuseras ultraljudsvågor till ett väldefinierat område i hjärnan, som hettas upp och lederas. Den transkraniella applikationen är i en utvecklingsfas och har introducerats i sjukvården vid 15 centra i världen. MRgFUS är ett icke-invasivt alternativ till neurokirurgi hos patienter som inte svarat på farmakologisk behandling. Metoden har applicerats vid essentiell tremor, Parkinsons sjukdom och vid tillstånd med neuropatisk smärta.

Syfte

Att studera huruvida MRgFUS är bättre eller lika bra som standardbehandling för essentiell tremor, neuropatisk smärta och Parkinsons sjukdom, avseende hälsorelaterad livskvalitet, Allmän daglig livsföring (ADL), symtomskattning och smärta.

Metoder

Systematisk litteratursökning gjordes och artiklar relevanta för frågeställningen granskades enligt mall och data extraherades. Evidensgradering av slutsatser gjordes enligt GRADE.

Resultat

Inga kontrollerade studier var publicerade. Fem fallserier inkluderades i rapporten. I samtliga analyser var de behandlade individerna sina egna kontroller; innan och upp till ett år efter behandling med MRgFUS. Dessutom jämfördes utfallet med tillståndens naturalförlopp. Randomiserade studier pågår och beräknas vara avslutade under hösten 2015.

Essentiell tremor studerades i tre små fallserier. Hälsorelaterad livskvalitet förbättrades, mätt som 70% reduktion på validerad livskvalitetskala för tremor. ADL förbättrades, mätt som 51-80% reduktion i en validerad tremorskala för ADL. Symtomskattning förbättrades, mätt som 39-85% reduktion på validerad skala för handtremor.

För samtliga utfall var det vetenskapliga underlaget otillräckligt (GRADE ⊕○○○).

Neuropatisk smärta studerades i en fallserie. Smärtskattning förbättrades, mätt som 41% reduktion på VAS-skala. Otillräckligt vetenskapligt underlag (GRADE ⊕○○○).

Parkinsons sjukdom studerades i en fallserie. Symptomskattning förbättrades, mätt som 61% reduktion på validerad skala för Parkinsons sjukdom.

Otillräckligt vetenskapligt underlag (GRADE ⊕○○○).

Komplikationer

Hittills har en allvarlig komplikation rapporterats; liten blödning och ischemi i lesionen. Lätta och övergående biverkningar förekom i anslutning till behandlingen. Långtidseffekter är inte studerade ännu.

Ekonomi

Investeringskostnader är höga; 14 miljoner SEK för MRgFUS utrustningen samt 20-25 miljoner SEK för MRI.

Sammanfattande bedömning

Det vetenskapliga underlaget för transkraniell MRgFUS är f.n. otillräckligt. För essentiell tremor var effekten omedelbar och bestående efter ett år. Även för neuropatisk smärta och Parkinsons sjukdom förbättrades smärta respektive symptom. Metoden har fördelen att vara icke-invasiv. Randomiserade studier för essentiell tremor och Parkinsons sjukdom förväntas bli klara om ett år. Långtidsuppföljning saknas. Investeringskostnaden är mycket hög.

The above summaries were written by HTA-centrum and approved by the Regional board for quality assurance of activity-based HTA. The Regional Health Technology Assessment Centre (HTA-centrum) Region Västra Götaland, Sweden has the task to make statements on HTA reports carried out in VGR. The English summary is a brief summary of similar outline as the summaries in the Cochrane systematic reviews. The Swedish summary addresses the question at issue, results including quality of evidence regarding efficacy and risks, economical and ethical aspects of the particular health technology that has been assessed in the report. The summary ends with a final statement and concluding remarks from HTA-centrum.

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3. Summary of Findings (SoF-table)

Outcomes	Study design Number of studies Total number of patients	Relative effect (95%CI)	Absolute effect	Certainty of evidence GRADE
Essential tremor				
Health Related Quality of Life (HRQoL)	1 case series n=15	Reduction 70% in Essential Tremor Questionnaire (QUEST) scores	37% to 11% at 12m, p=0.001	⊕○○○ Very low ¹
Activities of Daily Living (ADL)	3 case series n=30	Reduction 51% - 80% in clinical rating of score for tremor (CRST), part C disability	Study 1: Baseline-6m: 13-2.6, p=0.01 Study 2: Baseline-12m: 20.4-5.2, p=0.001 Study 3: Baseline-3m: 20.8-10.2, p=0.0106	⊕○○○ Very low ²
Symptom score	3 case series n=30	Reduction 39% - 85% in CRST scores, part B hand tremor	Study 1: Baseline-6m: 13.5-2.8, p=0.01 Study 2: Baseline-12m: 18.2-2.8, p=0.001 Study 3: Baseline-3m: 28.5-17.3, p=0.052	⊕○○○ Very low ²
Neuropathic pain				
Pain score	1 case series n=11	Reduction 41% in VAS	Baseline-12m: 59.5-35.3, p=0.033	⊕○○○ Very low ³
Parkinson's disease				
Symptom score	1 case series n=13	Reduction 61% in Unified Parkinson Disease Rating Scale (UPDRS)	39.8 to 15.6 at 3m, p=0.0001	⊕○○○ Very low ⁴

¹ Study design; uncontrolled study, comparison made with natural course of disease. Serious imprecision but large magnitude of effect.

² Study design; uncontrolled study, comparison made with natural course of disease. Uncertain precision but very large magnitude of effect.

³ Study design; uncontrolled study, comparison made with natural course of disease. Serious study limitations.

⁴ Study design; uncontrolled study, comparison made with natural course of disease. Serious indirectness and imprecision.

Certainty of evidence

High certainty ⊕⊕⊕⊕ We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty ⊕⊕⊕○ We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty ⊕⊕○○ Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty ⊕○○○ We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

4. Abbreviations

ADL	Activities of Daily Living
BBB	Blood-brain barrier
CRST	Clinical Rating Score for Tremor
DBS	Deep brain stimulation
HRQoL	Health Related Quality of Life
L-DOPA	Levodopa
MRI	Magnetic resonance imaging
MRgFUS	Magnetic Resonance guided Focused Ultrasound
PTT	Pallido-Thalamic Tract
QUEST	Quality of life in Essential Tremor Questionnaire
SCS	Spinal cord stimulation
STN	Subthalamic nucleus
UPDRS	Unified Parkinson's Disease Rating Scale
VAS	Visual Analogue Scale
VGR	Västra Götaland Regionen
VIM	Nucleus Ventralis Intermedius of the thalamus
VPL	Nucleus Ventralis Posterolateralis of the thalamus
VPM	Nucleus Ventralis Posteromedialis of the thalamus

5. Background

Disease/disorder of interest and its degree of severity

Essential tremor

Essential tremor is a disabling condition with implications on Activities in Daily Life (ADL) functions such as writing, eating, drinking, cooking and other activities requiring at least some steadiness of the hand. The quality of life can be severely reduced. Normally, the symptoms will aggravate with time. Remissions are not seen.

Neuropathic pain

Neuropathic pain includes a variety of conditions with chronic pain which is difficult to treat since ordinary analgesics often lack effect. A state of chronic pain reduces the quality of life. Patients with chronic neuropathic pain often seek help from various medical and para-medical units. Early retirement from work is common and some patients develop a drug abuse.

Parkinson's disease

Parkinson's disease is a degenerative neurologic disorder characterized by hypomotility, rigidity and tremor. Patients often have severe fluctuations in response to available drugs and the treatment of advanced Parkinson's disease is a challenge in neurology. Quality of life is reduced and the disease leads inevitably to permanent disability. The disease is progressive.

Prevalence and incidence

Essential tremor

The reported prevalence and incidence of essential tremor shows great variability. One study reported a prevalence between 0.4% and 3.9% and an incidence of 0.6% per year (Benito-Leon and Louis 2006). The incidence increases dramatically with age.

Neuropathic pain

The prevalence of neuropathic pain varies between 0.9% and 17.9% in different studies (Bouhassira et al. 2008). The incidence has been reported to be 0.82% per year (Dieleman et al., 2008). Estimates are uncertain due to different diagnostic criteria.

Parkinson's disease

Parkinson's disease has a prevalence of 0.12% and an annual incidence of 0.11% (Fall et al., 1996). The incidence increases dramatically with age.

Present treatment

Essential tremor

The first-hand pharmacological treatment for essential tremor is beta-blocking drugs (propranolol) or primidone. Patients not responsive to pharmacological treatment may be considered for advanced treatment. Deep brain stimulation (DBS) in the Nucleus Ventralis Intermedius of the thalamus (VIM) is currently used at the Department of Neurosurgery, Sahlgrenska University Hospital. Patients are referred from neurologists or general practitioners. Preoperative evaluation is done by the DBS-team (neurologists and neurosurgeons). Perioperatively the patient is hospitalised for three to four days. The DBS-equipment needs repetitive postoperative programming and must be replaced after four to five years.

Neuropathic pain

The treatment for neuropathic pain is primarily non-surgical. In advanced therapy-refractory cases surgery is considered, usually by spinal cord stimulation (SCS) or DBS. Patients are normally referred from units specialised in pain treatment. Target points for DBS are often the Nucleus Ventralis Posterolateralis (VPL) and Nucleus Ventralis Posteromedialis (VPM) of the thalamus, the periventricular gray and the periaqueductal gray. Perioperative hospitalisation and postoperative care are similar as for essential tremor.

Parkinson's disease

Advanced treatment for Parkinson's disease includes DBS, pumps for continuous Levodopa (L-DOPA) delivery into the duodenum and subcutaneous delivery of L-DOPA agonists. In the case of DBS the patient is hospitalised for about ten days. Postoperative follow up includes several sessions of programming of the DBS system. As for essential tremor and neuropathic pain the pulse generator needs replacement after four to five years.

The normal pathway through the health care system and current wait time for medical assessment /treatment

The waiting time for assessment at the Department of Neurology is normally less than three months. The time from assessment to treatment is about six months.

In a DBS procedure for essential tremor the patients are hospitalised for three days. At the day of arrival the stereotactic frame is mounted and the preoperative magnetic resonance imaging (MRI) scan is performed.

Surgery is performed the second day. Some patients are operated in local anaesthesia allowing immediate study of the effect on tremor in the operation room. Since it is an intracranial procedure the patients need neurological surveillance overnight but are discharged on the third day. After about two weeks they return to the hospital to start the pulse generator.

For patients with neuropathic pain the procedure is similar as for essential tremor.

Patients with Parkinson's disease are hospitalised for a longer period, about ten days, since the effect of DBS must be followed by reduced medication.

Number of patients per year who undergo current treatment regimen

On an annual basis about 20 patients, essential tremor being the most common diagnosis, are operated with DBS in the Region Västra Götaland.

Present recommendations from medical societies or health authorities

DBS is presently considered as a routine method in the treatment of essential tremor and advanced Parkinson's disease inpatients refractory to pharmacological treatment (policy document from the Swedish Movement Disorder Society). There are yet no recommendations regarding the new technology Magnetic Resonance guided Focused Ultrasound (MRgFUS).

6. Transcranial Magnetic Resonance Guided Focused Ultrasound

Magnetic resonance guided focused ultrasound (MRgFUS) is an advanced technique. In short, tcMRgFUS implies that ultrasound waves from a high number of transducers (elements) are focused towards a preoperatively defined target in the brain. The energy amount from one single element is not tissue damaging but in the focal point the temperature is elevated to a level where tissue destruction ensues. The process is monitored in real-time using MRI-thermometry, an MRI-protocol which visualizes the temperature in various parts of the brain overlaid on the anatomical image. MRI-thermometry can detect temperature differences in the order of a few degrees Celsius.

The biological effect of focused ultrasound is either thermal or mechanical (cavitation). Normally, cavitation is an unwanted effect, but in some cases a mechanical destruction of the tissue is beneficial. At frequencies around 650 kHz mainly thermal effects are achieved. Mechanical effects are more prominent at frequencies around 230 kHz.

The commercially available equipment for tcMRgFUS uses a helmet attached to the head via a stereotactic frame. The helmet contains 1024 transducers arranged in a hemisphere, quite similar in appearance to the gamma knife. A silicon membrane is attached around the shaved head of the patient and the space between the transducers and the skin is filled with degassed water to achieve cooling and good transduction. Devices for cooling the water and the ultrasound hardware are located next to the MRI scanner and the control unit is located in the MRI manoeuvre room.

During treatment, the MRI scanner continuously monitors the targeted area and surrounding structures. Due to the irregular form and thickness of the cranium there is a shift in phase between the ultrasound waves from the various elements. Since each element can be electronically controlled it is possible to adjust for this phase shift and focus the waves into a spot as small as 4 mm in diameter. Calcified structures, which may be hot foci, are excluded from the wave pathways. Initially, in order to detect the precise location of the intended target and to make necessary adjustments, non-ablative sonications are made with modest temperature elevations up to 40-41°C. Subsequently, the temperature is elevated to about 55°C where necrosis occurs. The system detects cavitation effects, and if this is the case the treatment is interrupted. Normally, the duration of the procedure is in the range of 3-4 hours. The procedure is conducted by neurosurgeons and physicists working together. The team also includes radiology, anaesthesiology and administrative personnel.

7. Objective

Question at issue:

In adults with treatment resistant essential tremor, neuropathic pain or Parkinson's disease, is transcranial MRgFUS better or as good as standard or no treatment concerning quality of life and ADL-function?

PICO P= Patients, I= Intervention, C= Comparison, O=Outcome

PICO 1

P = Adults with essential tremor refractory to medical treatment

I = Transcranial MRgFUS

C = Deep brain stimulation, placebo or no treatment

O =

Critical for decision making

Health related quality of life (HRQoL)

Activities of daily living (ADL)

Important but not critical for decision making

Symptom score

Complications

PICO 2

P = Adults with neuropathic pain refractory to medical treatment

I = Transcranial MRgFUS

C = Deep brain stimulation, placebo or no treatment

O =

Critical for decision making

Health related quality of life (HRQoL)

Activities of daily living (ADL)

Pain score

Important but not critical for decision making

Symptom score

Complications

PICO 3

P = Adults with Parkinson's disease refractory to medical treatment

I = Transcranial MRgFUS

C = Deep brain stimulation, placebo or no treatment

O =

Critical for decision making

Health related quality of life (HRQoL)

Activities of daily living (ADL)

Important but not critical for decision making

Symptom score validated for Parkinson's disease (UPDRS)

Complications

8. Methods

The activity based HTA-process

Systematic literature search (Appendix 1)

During March 2015 two authors (JP, ELD) performed systematic searches in PubMed, Embase, the Cochrane Library, and a number of HTA-databases. Reference lists of relevant articles were also scrutinised for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1. These authors conducted the literature searches and selected studies. Independently of one another they assessed the obtained abstracts and made a first selection of full-text articles for inclusion or exclusion. Any disagreements were resolved in consensus. The remaining articles were sent to all the participants of the project group. They read the articles independently of one another. It was finally decided in a consensus meeting which articles should be included in the assessment.

Critical appraisal and certainty of evidence

The included studies and their design and patient characteristics are presented in Appendix 2. The excluded studies and the reasons for exclusion are presented in Appendix 3. The included studies have been critically appraised using a checklist for assessment of case series, modified from Guo et al (2013) by HTA-centrum. The results and the assessed quality of each article have been summarised per outcome in Appendix 4. A summary result per outcome and the associated certainty of evidence are presented in a Summary-of-findings table (page 6). The certainty of evidence was defined according to the GRADE system (Atkins et al, 2004; GRADE Working group).

Ongoing research

A search for ongoing studies was conducted in clinicaltrials.gov (2015-04-29) using the search terms (MRgFUS OR MRgHIFU OR MR-HIFU OR “Magnetic resonance-guided focused ultrasound” OR “Magnetic resonance-guided high-intensity focused ultrasound”) OR ((FUS OR Focused ultrasound surgery OR High-intensity focused ultrasound* OR HIFU OR Thermoablative therap* OR Thermal ablat*) AND (MR OR MRI OR MR-Imaging OR MR Imaging OR Magnetic Resonance imaging)) AND (Transcranial OR Trans-cranial OR Intra-cranial OR Intracranial) OR TcMRgFUS.

9. Results

Literature search (Appendix 1)

The literature search identified a total of 217 articles (after removal of duplicates). Two authors (JP, ELD) excluded 185 articles after reading their abstracts. Another 17 articles were excluded after reading the articles in full text. The remaining 15 articles were sent to all authors, and five articles concurrent with the PICO were finally included in the assessment. All articles were case series using a before-after design. The evaluation of the treatment effect included also a comparison with the natural course of the disorder.

Results per outcome

MRgFUS for treatment of patients with essential tremor (PICO 1)

Critical outcomes

Health Related Quality of Life (Appendix 4.1)

The effect of MRgFUS was studied in one case-series (n=15) with low to moderate risk of bias. An increase in HRQoL was reported, measured as a reduction in Quality of life in Essential Tremor Questionnaire (QUEST) scores (from 37% to 11%, p=0.001) at one year after treatment. This implies an improvement in HRQoL compared with the natural course of the disease.

Conclusion: It is uncertain whether MRgFUS treatment improves HRQoL in patients with essential tremor. Very low certainty of evidence (GRADE ⊕○○○).

Activities of Daily Living (ADL) (Appendix 4.2)

The effect of MRgFUS in essential tremor was studied in three case-series with low to moderate risk of bias, including a total of 30 patients. The case-series reported a reduction by more than half in clinical rating of score for tremor (CRST), part C disability, which was statistically significant in the two largest case-series (p=0.011 and p=0.001) at six and twelve months follow up. This implies a large improvement in ADL function compared with the natural course of the disease.

Conclusion: It is uncertain whether MRgFUS treatment improves ADL in patients with essential tremor. Very low certainty of evidence (GRADE ⊕○○○).

Important outcomes

Symptom score (Appendix 4.3)

The effect of MRgFUS in essential tremor was studied in three case-series with low to moderate risk of bias, including a total of 30 patients. The case-series reported a reduction by more than half in CRST scores, part B hand tremor, which was statistically significant in the two largest case-series (p=0.011 and p=0.001), at six and twelve months follow up. The effect was immediate and sustainable. This implies a clinically relevant reduction of hand tremor in patients with essential tremor compared with the natural course of the disorder.

Conclusion: It is uncertain whether MRgFUS treatment reduces hand tremor. Very low certainty of evidence (GRADE ⊕○○○).

MRgFUS for treatment of patients with neuropathic pain (PICO 2)

Critical outcomes

The outcomes **Health Related Quality of Life** and **Activities of Daily Living** were not reported

Pain score (Appendix 4.4)

The effect of MRgFUS was studied in one case-series (n=11) with high risk of bias. A 40% reduction (p=0.033) in pain was reported, as measured with Visual Analogue Scale (VAS) at one year after treatment.

Conclusion: It is uncertain whether MRgFUS treatment reduces pain in patients with neuropathic pain. Very low certainty of evidence (GRADE ⊕○○○).

Important outcomes

The outcome **symptom score** was not reported

MRgFUs for treatment of patients with Parkinson's disease (PICO 3)

Critical outcomes

The outcomes **Health Related Quality of Life** and **Activities of Daily Living** were not reported

Important outcomes

Symptom score (Appendix 4.5)

The effect of MRgFUS in Parkinson's disease was studied in one case-series (n=13) with moderate risk of bias. It reported a reduction from 39.8 to 15.6 (p=0.0001) in Unified Parkinson Disease Rating Scale (UPDRS), (maximum 147) at three months follow-up.

Conclusion: It is uncertain whether MRgFUS treatment reduces symptoms in Parkinson's disease compared with the natural course of the disease. Very low certainty of evidence (GRADE ⊕○○○).

Complications associated with MRgFUS treatment (PICO 1-3)

The most serious complication was a small bleeding in the target, with ischemia in motor thalamus, in one patient treated for neuropathic pain.

During the procedure, many patients had a sense of warmth superficially on the scalp. Transient sensations of dizziness and nausea were common.

Patients treated for essential tremor often had transient paraesthesia in the fingers.

After one year most of the symptoms had disappeared.

10. Ethical consequences

MRgFUS treatment complies well with most ethical demands. It is less invasive than present neurosurgical methods and less likely to cause complications. Two ethical problems are identified. The first is the very low certainty of evidence, despite the reported positive effects in case series. Long term effects have not been studied. This problem might be overcome in the future, if clinical controlled trials confirm a positive effect. The second problem is the high initial cost of the equipment, which may have negative implications on other technology investments as well as displacement effects (Appendix 5).

11. Organisation

The use of transcranial MRgFUS requires the Exablate Neuro equipment (Insightec). The procedure also requires access to a 3T MRI scanner (General Electric). This type of MRI scanner is presently installed at the Radiology Department at Queen Silvia Children's Hospital (Gothenburg), but will be fully utilised for diagnostic imaging. We therefore believe that introduction of MRgFUS would require an investment of a new 3T MRI scanner from General Electric.

The procedure takes place in the MRI scanner and does not need a fully equipped operation room. Normally, patients are awake during the procedure and anaesthesiology equipment is therefore not needed. Access to a preparatory room for shaving and mounting of the stereotactic frame is necessary. The Exablate Neuro Hardware can be suited in the scanner room and the manoeuvre room.

Present use of MRgFUS in other hospitals

The Academic Hospital in Uppsala has recently installed MRgFUS equipment for extracranial use. There is no tcMRgFUS equipment in Scandinavia. There are about 15 tcMRgFUS installations worldwide.

Consequences of MRgFUS for personnel

There will be a need for education of the personnel involved in the maintenance and handling of the MRgFUS equipment, mainly physicians and engineers. MRI-personnel will need some additional education.

Consequences for other clinics or supporting functions at the hospital or in the Region Västra Götaland

Since MRgFUS is an entirely new technology that offers a treatment option for patient categories which presently cannot be treated at all, it is likely that the number of referred patients will increase. However, since MRgFUS is a non-invasive procedure with a minimal requirement for pre- and postoperative care, the need for in-hospital care will probably be low.

12. Economic aspects

Costs of currently used health technology

Essential tremor

Cost per patient diagnosed with essential tremor (ICD-10: G25) and treated with Deep Brain Stimulation (DBS) (surgery code AAG20) is SEK 170,000. The DBS treatment is performed at the Sahlgrenska University Hospital and in 2013 and 2014, nine and seven procedures were performed respectively. The pulse generator needs to be replaced on average every four to five years (surgery code AEA00) with an average cost of SEK 86,000. In 2013 and 2014, three and four replacements were performed respectively. Cost per patient for the DBS treatment and replacements of pulse generator includes health care personnel, material cost, theatre costs and costs of inpatient care after surgery as well as overhead costs.

Neuropathic pain

Cost for the DBS treatment for a patient diagnosed with neuropathic pain is comparable to essential tremor treatments, but the number of patients is even lower.

Parkinson's disease

Cost per patient diagnosed with Parkinson's disease (ICD-10: G20) and treated with DBS (surgery code AAG20) is SEK 177,000. In 2013 and 2014, two procedures were performed respectively. The pulse generator needs to be replaced on average every four to five years (surgery code AEA00) with an average cost of SEK 135,000. In 2013 and 2014, five replacements were performed respectively. Cost per patient is somewhat higher for patients with Parkinson's disease due to patients are hospitalised for a longer period since the effect of the DBS must be followed by reduced medication.

The annual costs for the year 2014 is estimated to SEK 2.56 million based on procedures per year

Expected costs of MRgFUS

The total investment cost of MRgFUS is estimated to SEK 40 million. With a deprivation at 7 years (recommended by "Landstingsförbundet" for medical technology) the annual cost is SEK 5.7 million. Based on the assumption of a capacity to treat three patients per week during 40 weeks per year with MRgFUS, the cost per patient is estimated to SEK 48 000. The capacity will increase with time when the process becomes more familiar to the medical personnel, estimated to one or two patients per day.

Total change of cost

When only considering the investment costs, the MRgFUS is a less costly alternative when comparing with a DBS treatment based on cost per patient. However, initially there is a need of education for the medical personnel and change of current work processes. Based on an estimation of low capacity during the learning period, the cost per patient is SEK 48 000 compared to treatment with DBS with a cost per patient of SEK 170 000 to 177 000 and change of pulse generator every five years with a cost per patient of SEK 86 000 to 135 000.

Possibility to adopt and use MRgFUS within the present budget

Not possible.

Available evidence of cost-effectiveness analyses or cost advantages or disadvantages

There are no available health economic analyses on the topic.

13. Discussion

The present HTA analysis is based on three case series (n=30 in total) on MRgFUS treatment for essential tremor, one case series (n=11) on MRgFUS treatment in neuropathic pain and one case series (n=13) on MRgFUS treatment in Parkinson's disease.

Small case series contribute by default to very low certainty of evidence. Although favourable effects were seen within the studied groups, the conclusions ended up in 'very low' confidence in the effect estimates of the reported outcomes. This is commonly seen for new treatment modalities where controlled clinical trials have not yet been completed.

The ideal head-to-head comparisons between DBS and MRgFUS are not available. The natural course of essential tremor is well known, and it leads to progressive deterioration. Available case series where MRgFUS treatment is used, suggest that almost every patient is improved. These results are comparable to the effect of DBS.

The results for the neuropathic pain and the Parkinson's disease patients were less consistent. This is in line with the experience from DBS treatment.

In addition to being an alternative for patients currently treated with DBS, MRgFUS also makes it possible to treat patients who presently cannot be offered any treatment, due to increased risk of bleeding, wide subarachnoid spaces and/or widened ventricles.

In parallel with the introduction of a new technology it is always important to systematically follow up and evaluate patient benefits and adverse outcomes. For the addressed MRgFUS treatment of essential tremor, neuropathic pain and Parkinson's disease, the patient related outcomes remain to be evaluated. The available case series can be considered as feasibility studies of a newly developed technology. It is currently not known if this treatment has any long-term adverse effects. Initial positive effects from intended brain lesions, may have unpredictable negative long term effects. Thus, long term follow-up of these treatments are mandatory.

14. Future perspectives

Scientific knowledge gaps

Since the MRgFUS technology still is new there are many knowledge gaps. All outcomes of the three disorders in this report need further evaluation. Much research is still at the experimental level. The clinical use of transcranial MRgFUS has so far been restricted to the diagnoses that have been the focus in this report, plus a few case reports on the treatment of glioblastoma and obsessive-compulsive disease.

The method has a potential for further development, and there is ongoing research within several fields of neurology and oncology. Stroke and brain tumours are of particular interest. In the case of ischemic stroke, MRgFUS can be used alone or in combination with pharmacological thrombolysis, followed by an evacuation with a minimally invasive neurosurgical technique. Transcranial MRgFUS may temporarily open the blood-brain barrier, which could imply a paradigm shift with regard to pharmacological and/or immunological treatment of intracerebral diseases.

Other possible future targets for tcMRgFUS are epilepsy, hydrocephalus and trigeminal neuralgia. transcranial MRgFUS may also enable the targeted delivery of stem cells into various brain regions in the treatment of degenerative neurological diseases such as Alzheimer's disease and Huntington's disease.

Ongoing research

A search for ongoing studies ([Clinicaltrials.gov](https://clinicaltrials.gov)) identified 62 trials, of which 12 were relevant for the question at issue.

Particularly two RCTs are of interest, comparing MRgFUS with sham procedure in patients with essential tremor (NCT01827904) and Parkinson's disease (NCT01772693), respectively.

Essential tremor

NCT01932463: Single-group feasibility study to evaluate safety and initial effectiveness of ExAblate MRgFUS for unilateral thalamotomy in the treatment of tremor. Status: Completed – No study results posted.

NCT01827904: Randomised, double-blind trial (to subjects, local site's blinded assessor and tremor Core Lab assessors), multi-site (ExAblate treated arm Vs ExAblate sham treated control arm) to test the efficacy of treatment using the ExAblate transcranial system and to further demonstrate safety in medication-refractory tremor in subjects with essential tremor. Status: Ongoing but not recruiting participants. Estimated Study Completion Date: September 2015.

NCT02289560: Single-group study with objective to capture the efficacy of treatment using the ExAblate transcranial system and to further demonstrate safety in medication-refractory tremor in patients with essential tremor. Status: Recruiting participants.

NCT02037217: Single-group feasibility study to evaluate safety and initial effectiveness of ExAblate transcranial MRgFUS treatment of patients with medication-refractory movement disorders, namely essential tremor. Status: Ongoing but not recruiting participants.

NCT01304758: Single-group study to evaluate the safety and initial effectiveness of MRI-guided focused ultrasound thermal ablation of a designated area in the brain of patients suffering from medication-refractory essential tremor, using the ExAblate transcranial system. Status: Completed – No study results posted.

Neuropathic Pain

NCT01699477: Single-group (functional brain disorders /neuropathic pain) study to assess the efficacy and the clinical safety of the transcranial magnetic resonance guided high intensity focused ultrasound system ExAblate 4000, InSightec Ltd. for functional neurosurgery. Status: recruitment status of this study is unknown.

Parkinson's disease

NCT02347254: Single-group study evaluating the safety and initial effectiveness of the ExAblate transcranial MRgFUS) treatment of patients with L-dopa induced dyskinesia of Parkinson's disease. Status: Recruiting participants.

NCT02263885: Single-group study evaluating the safety, and initial efficacy of using the ExAblate transcranial to create a unilateral lesion in the globus pallidus as an adjunct to Parkinson's disease medications in subjects who are over 30 years of age and considered medication-refractory with advanced idiopathic Parkinson's disease. Status: Recruiting participants.

NCT02246374: Single-group study. Advanced idiopathic Parkinson's disease. This is primarily a safety protocol to evaluate the safety of unilateral subthalamotomy using transcranial ExAblate in a staged, escalating dose titration manner; Stage I is subtherapeutic; Stage II is full, therapeutic unilateral lesioning. Status: Recruiting participants.

NCT01772693: Randomised double blind trial. A feasibility study to evaluate the safety and initial effectiveness of unilateral ExAblate thermal ablation of the Vim thalamic nucleus of subjects suffering from medication-refractory, idiopathic, tremor-dominant Parkinson's disease, using the ExAblate transcranial system compared to a sham Vim thalamotomy procedure. Status: Recruiting participants. Estimated Primary Completion Date: September 2015 (Final data collection date for primary outcome measure)

NCT02003248: Single-group study. The proposed study is to evaluate the safety and initial effectiveness of the ExAblate transcranial MRI-guided focused ultrasound (MRgFUS) treatment of patients with dyskinesia of Parkinson's Disease. Status: Recruiting participants.

Mixed populations

NCT01698450: Single-group study (essential tremor, dystonia, Parkinson's Disease) to assess the efficacy and the clinical safety of the transcranial magnetic resonance guided high intensity focused ultrasound system ExAblate 4000, InSightec Ltd. for functional neurosurgery in the treatment of movement disorders. Status: Completed – No study results posted.

Interest at the clinic/research group/organisation to start studies/trials within the research field at issue

There is a large interest to conduct research in this area, but the equipment is a prerequisite for conducting studies.

15. Participants in the project.

The question was nominated by

Goran Delic, Head of the Department of Neurosurgery, Sahlgrenska University Hospital, Göteborg, Sweden.

Participants from the clinical departments

Olle Corneliussen, M.D., Ph.D., Department of Neurosurgery, Sahlgrenska University Hospital

Thomas Björk-Eriksson, M.D., Ph.D., Associate professor, Department of Oncology, Sahlgrenska University Hospital

Andreas Fhager, Associate professor, Department of Signals and Systems, Chalmers University of Technology, Göteborg Sweden.

Ina Skagervik, M.D., Department of Neurosurgery, Sahlgrenska University Hospital

Participants from the HTA-centrum

Annika Strandell, Associate professor

Petteri Sjögren, DDS, PhD

Josefine Persson, MSc, Health economist

Eva-Lotte Daxberg, librarian

Jonas Pettersson, librarian

External reviewers

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Anders I. Larsson MD, PhD, Consultant Neurologist, Research and Development Unit, Södra Älvsborg Hospital, Neurology- and Rehab Clinic, Neurology Department

Conflicts of interest

None

Project time

HTA was accomplished during the period of 2015-03-05 – 2015-09-30

Literature searches were made in March 2015

Appendix 1, Search strategy, study selection and references

Question(s) at issue:

In adults with treatment resistant essential tremor, neuropathic pain or Parkinson's disease, is transcranial MRgFUS better or as good as standard or no treatment concerning quality of life and ADL-function?

PICO (*P=Patient I=Intervention C=Comparison O=Outcome*)

PICO 1

P = Adults with essential tremor refractory to medical treatment

I = Transcranial MRgFUS

C = Deep brain stimulation, placebo or no treatment

O = Critical for decision making
Health related quality of life (HRQoL)
Activities of daily living (ADL)

Important but not critical for decision making
Symptom score

Complications

PICO 2

P = Adults with neuropathic pain refractory to medical treatment

I = Transcranial MRgFUS

C = Deep brain stimulation, placebo or no treatment

O = Critical for decision making
Health related quality of life (HRQoL)
Activities of daily living (ADL)
Pain score

Important but not critical for decision making
Symptom score

Complications

PICO 3

P = Adults with Parkinson's disease refractory to medical treatment

I = Transcranial MRgFUS

C = Deep brain stimulation, placebo or no treatment

O = Critical for decision making
Health related quality of life (HRQoL)
Activities of daily living (ADL)

Important but not critical for decision making
Symptom score validated for Parkinson's disease (UPDRS)

Complications

Eligibility criteria

Study design

All types of published studies

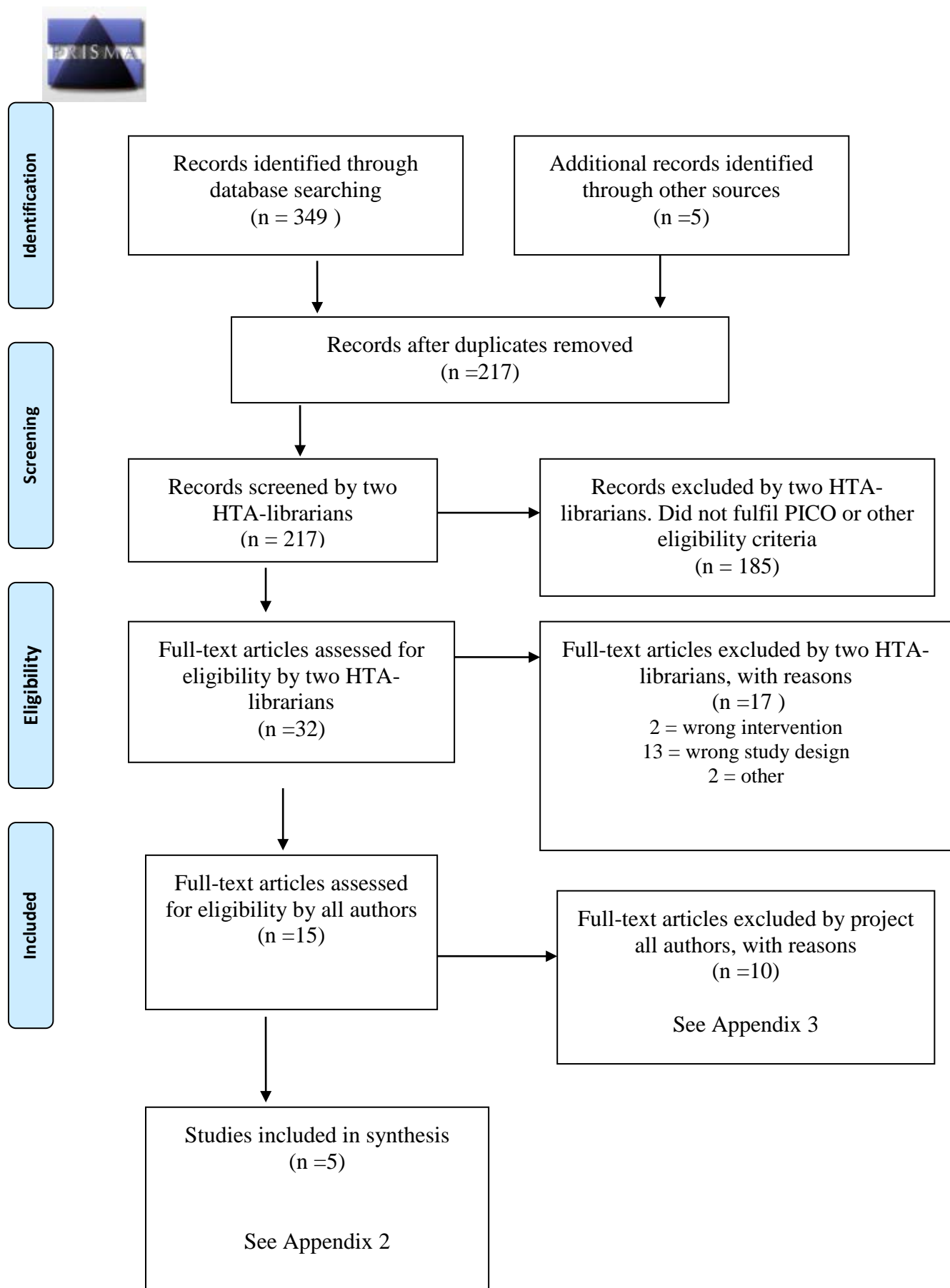
Publication date:

No limitation

Language:

English, Swedish, Norwegian, Danish

Selection process – flow diagram



Search strategies

Database: PubMed

Date: 2015-03-08

No of results: 160

Search	Query	Items found
#20	Search #13 NOT #14 Filters: Danish; English; Norwegian; Swedish	160
#14	Search (Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp])	1383133
#13	Search #11 NOT #12	174
#12	Search ((animals[mh]) NOT (animals[mh] AND humans[mh]))	3979742
#11	Search #9 OR #10	209
#10	Search Exablate[tiab] OR Sonablate[tiab] OR Ablatherm[tiab] OR Insightec[tiab]	123
#9	Search #7 OR #8	92
#8	Search TcMRgFUS[tiab]	8
#7	Search #5 AND #6	89
#6	Search Transcranial[tiab] OR Trans-cranial[tiab] OR Intra-cranial[tiab] OR Intracranial[tiab]	100187
#5	Search #1 OR #4	1305
#4	Search #2 AND #3	1251
#3	Search Magnetic Resonance Imaging[mh] OR Magnetic Resonance Imaging, Interventional[mh] OR MR[tiab] OR MRI[tiab] OR MR-Imaging[tiab] OR MR Imaging[tiab] OR Magnetic Resonance imaging[tiab]	447068
#2	Search FUS[tiab] OR Focused ultrasound surgery[tiab] OR High-Intensity Focused Ultrasound Ablation[mh] OR Ultrasonic therapy[mh] OR High-intensity focused ultrasound*[tiab] OR HIFU[tiab] OR Thermoablative therap*[tiab] OR Thermal ablat*[tiab]	12641
#1	Search MRgFUS[tiab] OR MRgHIFU[tiab] OR MR-HIFU[tiab] OR Magnetic resonance-guided focused ultrasound[tiab] OR Magnetic resonance-guided high-intensity focused ultrasound[tiab]	293

Database: EMBASE (1980 to Present)

Date: 2015-03-08

No of results: 162

Searches		Results
1	(MRgFUS or MRgHIFU or MR-HIFU or "Magnetic resonance-guided focused ultrasound" or "Magnetic resonance-guided high-intensity focused ultrasound").ti,ab.	389
2	exp ultrasound therapy/	18672
3	exp high intensity focused ultrasound/	2937
4	(FUS or "Focused ultrasound surgery" or "High-intensity focused ultrasound ablation" or HIFU or Thermoablative ther* or Thermal ablat*).ti,ab.	6594
5	2 or 3 or 4	23143
6	(MR or MRI or "MR-Imaging" or "MR Imaging" or "Magnetic Resonance imaging").ti,ab.	415846

7	exp nuclear magnetic resonance imaging/	579504
8	6 or 7	656589
9	5 and 8	2369
10	1 or 9	2464
11	(Transcranial or Trans-cranial or Intra-cranial or Intracranial).ti,ab.	124016
12	10 and 11	119
13	TcMRgFUS.ti,ab.	11
14	12 or 13	126
15	(Exablate or Sonablate or Ablatherm or Insightec).ti,ab.	305
16	14 or 15	422
17	limit 16 to (animals and animal studies)	31
18	16 not 17	391
19	limit 18 to (danish or english or norwegian or swedish)	365
20	limit 19 to (article or erratum or "review")	162

Database: The Cochrane Library

Date: 2015-03-08

No of results: 27

Cochrane reviews 10

Other reviews 1

Trials: 4

Technology assessments 11

Economic evaluations 1

#	Searches	Results
#1	MRgFUS or MRgHIFU or MR-HIFU or Magnetic resonance-guided focused ultrasound or Magnetic resonance-guided high-intensity focused ultrasound	23
#2	FUS or Focused ultrasound surgery or High-intensity focused ultrasound* or HIFU or Thermoablative therap* or Thermal ablat*	709
#3	MeSH descriptor: [Ultrasonic Therapy] explode all trees	754
#4	MeSH descriptor: [High-Intensity Focused Ultrasound Ablation] explode all trees	55
#5	#2 or #3 or #4	1371
#6	MR or MRI or MR-Imaging or MR Imaging or Magnetic Resonance imaging	22988
#7	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees	5741
#8	MeSH descriptor: [Magnetic Resonance Imaging, Interventional] explode all trees	18
#9	#6 or #7 or #8	23087
#10	#5 and #9	144

#11	#1 or #10	149
#12	Transcranial or Trans-cranial or Intra-cranial or Intracranial	6923
#13	#11 and #12	12
#14	TcMRgFUS	0
#15	Exablate or Sonablate or Ablatherm or Insightec	16
#16	#13 or #15	27

Database: CRD
Date: 2015-03-08
No of results: 0

Line	Search	Hits
1	(MRgFUS OR MRgHIFU OR MR-HIFU OR Magnetic resonance-guided focused ultrasound OR Magnetic resonance-guided high-intensity focused ultrasound)	9
2	(FUS OR Focused ultrasound surgery OR High-intensity focused ultrasound* OR HIFU OR Thermoablative therap* OR Thermal ablat*)	66
3	(MR OR MRI OR MR-Imaging OR MR Imaging OR Magnetic Resonance imaging)	1683
4	MeSH DESCRIPTOR magnetic resonance imaging EXPLODE ALL TREES	792
5	MeSH DESCRIPTOR magnetic resonance imaging, interventional EXPLODE ALL TREES	10
6	#3 OR #4 OR #5	1732
7	#2 AND #6	12
8	#1 OR #7	16
9	(Transcranial OR Trans-cranial OR Intra-cranial OR Intracranial)	692
10	#8 AND #9	0
11	(TcMRgFUS)	0
12	(Exablate OR Sonablate OR Ablatherm OR Insightec)	13
13	#8 OR #12	22
14	#9 AND #13	0

The web-sites of **SBU, Kunnskapssenteret** and **Sundhedsstyrelsen** were visited 2015-03-08. Nothing relevant to the question at issue was found

Reference lists

A comprehensive review of reference lists brought 5 new records. One of them was relevant for our PICO.

Reference lists

Included studies:

Chang WS, Jung HH, Kweon EJ, Zadicario E, Rachmilevitch I, Chang JW. Unilateral magnetic resonance guided focused ultrasound thalamotomy for essential tremor: practices and clinicoradiological outcomes. *J Neurol Neurosurg Psychiatry*. 2015a;86(3):257-64.

Elias WJ, Huss D, Voss T, Loomba J, Khaled M, Zadicario E, et al. A pilot study of focused ultrasound thalamotomy for essential tremor. *N Engl J Med*. 2013;369(7):640-8.

Jeanmonod D, Werner B, Morel A, Michels L, Zadicario E, Schiff G, et al. Transcranial magnetic resonance imaging-guided focused ultrasound: noninvasive central lateral thalamotomy for chronic neuropathic pain. *Neurosurg Focus*. 2012 Jan;32(1):E1. doi: 10.3171/2011.10.FOCUS11248.

Lipsman N, Schwartz ML, Huang Y, Lee L, Sankar T, Chapman M, et al. MR-guided focused ultrasound thalamotomy for essential tremor: a proof-of-concept study. *Lancet Neurol*. 2013;12(5):462-8.

Magara A, Buhler R, Moser D, Kowalski M, Pourtehrani P, Jeanmonod D. First experience with MR-guided focused ultrasound in the treatment of Parkinson's disease. *J Ther Ultrasound*. 2014;2:11.

Excluded studies:

Anzai Y, Lufkin R, DeSalles A, Hamilton DR, Farahani K, Black KL. Preliminary experience with MR-guided thermal ablation of brain tumors. *AJNR Am J Neuroradiol*. 1995;16(1):39-48; discussion 9-52.

Chang JW, Min BK, Kim BS, Chang WS, Lee YH. Neurophysiologic correlates of sonication treatment in patients with essential tremor. *Ultrasound Med Biol*. 2015b;41(1):124-31.

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Martin E, Jeanmonod D, Morel A, Zadicario E, Werner B. High-intensity focused ultrasound for noninvasive functional neurosurgery. *Ann Neurol*. 2009;66(6):858-61.

McDannold N, Clement GT, Black P, Jolesz F, Hynynen K. Transcranial magnetic resonance imaging-guided focused ultrasound surgery of brain tumors: initial findings in 3 patients. *Neurosurgery*. 2010;66(2):323-32; discussion 32.

Ram Z, Cohen ZR, Harnof S, Tal S, Faibel M, Nass D, et al. Magnetic resonance imaging-guided, high-intensity focused ultrasound for brain tumor therapy. *Neurosurgery*. 2006;59(5):949-55; discussion 55-6.

Wintermark M, Druzgal J, Huss DS, Khaled MA, Monteith S, Raghavan P, et al. Imaging findings in MR imaging-guided focused ultrasound treatment for patients with essential tremor. *AJNR Am J Neuroradiol*. 2014a;35(5):891-6.

Wintermark M, Huss DS, Shah BB, Tustison N, Druzgal TJ, Kassell N, et al. Thalamic connectivity in patients with essential tremor treated with MR imaging-guided focused ultrasound: in vivo fiber tracking by using diffusion-tensor MR imaging. *Radiology*. 2014b;272(1):202-9.

Other references:

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ*. 2004 Jun 19;328(7454):1490-4.

Benito-León J, Louis ED. Essential tremor: emerging views of a common disorder. *Nat Clin Pract Neurol*. 2006 Dec;2(12):666-78; quiz 2p following 691.

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Available from: <https://www2.sahlgrenska.se/upload/SU/HTA-centrum/Hj%c3%a4lpmedel%20under%20projektet/Granskningsmall%20f%c3%b6r%20fallserier%202015-03-25.docx>

Dieleman JP, Kerklaan J, Huygen FJ, Bouma PA, Sturkenboom MC. Incidence rates and treatment of neuropathic pain conditions in the general population. *Pain*. 2008 Jul 31;137(3):681-8.

Fall PA, Axelson O, Fredriksson M, Hansson G, Lindvall B, Olsson JE, et.al. Age-standardized incidence and prevalence of Parkinson's disease in a Swedish community. *J Clin Epidemiol*. 1996 Jun;49(6):637-41.

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Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009 Jul 21;6(7):e1000097.

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Appendix 2 – Included studies – design and patient characteristics.

Author, year,	Country	Study Design	No of participants mean age, years (SD)	% men	Treated condition/disease PICO 1-3	Outcomes
Chang, 2015a	Korea	Case-series	11 64.8 (7.7)	82	Essential tremor PICO 1	CRST/ADL Complications
Elias, 2013	USA	Case-series	15 66.6 (8.0)	67	Essential tremor PICO 1	Quality of life CRST/hand tremor CRST/disability (ADL)
Jeanmonod, 2012	Switzerland	Case-series	12 range 45-75	Not reported	Neuropathic pain PICO 2	VAS score/Pain relief Complications
Lipsman, 2013	Canada	Case-series	4 age not reported	100	Essential tremor PICO 1	CRST/hand tremor CRST/ADL Complications
Magara, 2009	Switzerland	Case-series	13 64.5 (12.8)	62	Parkinson's disease PICO 3	UPDRS score (Complications, only technical according to MRI)

CRST = clinical rating of Score for Tremor (range 0-160, with higher scores indicating greater perceived disability)

SD = standard deviation

Project: MRgFUS
Appendix 3. Excluded articles

Study author, publication, year	Reason for exclusion
Anzai, 1995	Wrong intervention (not MRgFUS)
Chang, 2015b	Wrong outcome
Coluccia, 2014	Wrong patient group (tumors)
Daffertshofer, 2005	Wrong intervention (not MRgFUS)
Jung, 2015	Wrong outcome (no patient related outcomes)
Martin, 2009	Duplicate report with Jeanmonod, 2012
McDannold, 2010	Wrong patient group (tumors)
Ram, 2006	Wrong intervention (not MRgFUS)
Wintermark. 2014a	Duplicate report with Elias, 2013
Wintermark. 2014b	Duplicate report with Elias, 2013

Table 4.1 MRgFUS for treatment of essential tremor (PICO 1)

Outcome variable: Quality of life

* + No problem
 ? Some problems
 - Major problems

Author, year	Country	Study design	Number of patients	With drawals - dropouts	Result MRgFUS	Comments	Directness*	Study limitations*	Precision*
Elias, 2013	USA	Case-series	15	0	Baseline: 37 % 12 months: 11 % p = 0.001	Quality of life in Essential Tremor Questionnaire (QUEST)*	+/?	+/?	-

*Quality of life in Essential Tremor Questionnaire (QUEST) score ranging from 0-100%, with higher percentage scores indicating greater perceived disability.

Table 4-2. MRgFUS for treatment of essential tremor (PICO 1)

Outcome variable: ADL

* + No problem
 ? Some problems
 - Major problems

Author, year	Country	Study design	Number of patients	With drawals - dropouts	Result MRgFUS Mean (SD) if not otherwise stated	Comments	Directness*	Study limitations *	Precision*
Chang, 2014	Korea	Case-series	11	3 (tech failure)	CRST Baseline: 13.5 (4.0) 1 month: 3.1 (3.6) 3 months: 3.1 (3.8) 6 months: 2.8 (3.5) p=0.011	CRST Part C	+/?	+/?	-
Elias, 2013	USA	Case-series	15	0	CRST Baseline: 18.2 (4.1) 1 yr: 2.8 (3.4) p=0.001 Physical Performance test Baseline: 22.9 (3.0) 1 yr: 27.1 (2.7) p= 0.001	CRST Part C 0-32, higher score indicating better performance	+/?	+/?	-
Lipsman, 2013,	Canada	Case-series	4	0	CRST Baseline: 20.8 (4.5) 1 month: 8.0 (4.2) 3 months: 10.2 (3.3), p=0.0106*	Calculated from individual results presented in the article	+/?	+/?	-

CRST = Clinical rating of Score for Tremor, Part C disability (ADL, Activity of daily living), range 0-32, higher scores indicating worse disability.

*calculated on aggregated data using unpaired Student's t-test (individual data not available), thus underestimating statistical significance.

Table 4.3 MRgFUS for treatment of essential tremor (PICO 1)

Outcome variable: Symptom score

* + No problem
 ? Some problems
 - Major problems

Author, year	Country	Study design	Number of patients	With draws - dropouts	Result MRgFUS Mean (SD) if not otherwise stated	Comments	Directness*	Study limitations*	Precision*
Chang, 2015	Korea	Case-series	11		<u>Hand tremor</u> Baseline: 13 (3.2) 1 month: 3.3 (3.3) 3 months: 3.5 (3.6) 6 months: 2.6 (3.1) p =0.011	Measured as CRST (Part B) drawing writing - Rt. Hand. 0-32	+/?	+/?	-
Elias, 2013	USA	Case-series	15	0	<u>Hand tremor</u> Baseline: 20.4 (5.2) 3 months: 4.3 (3.5) 12 months: 5.2 (4.8) p = 0.001	CRST, for hand tremor 0-32	+/?	+/?	-
Lipsman, 2013	Canada	Case-series	4	0	<u>Hand tremor</u> Baseline: 28.5 (6.5) 1 month: 16.0 (7.6) 3 months: 17.3 (6.6), p=0.052* p not presented in article	CRST 0-36 (as presented by the authors)	+/?	+/?	-

CRST = Clinical rating of Score for Tremor, Part B component contralateral hand tremor.

*calculated on aggregated data using unpaired Student's t-test (individual data not available), thus underestimating statistical significance.

Table 4.4 MRgFUS for treatment of neuropathic pain (PICO 2)

Outcome variable: Pain score (VAS)

* + No problem
 ? Some problems
 - Major problems

Author, year	Country	Study design	Number of patients	With drawals - dropouts	Result MRgFUS Mean (SD) if not otherwise stated	Comments	Directness*	Study limitations *	Precision*
Jeanmonod, 2012	Switzerland	Case-series	11	3 (2 tech failures, 1 death at 1 year)	Baseline: 59.5 (11.3) 3 months: 34.3 (23.3) 1 year: 35.3 (26.7) p = 0.0333*	VAS 0-100, higher score indicating more pain	-	?-	-

*calculated on aggregated data using unpaired Student's t-test (individual data not available), thus underestimating statistical significance.

Table 4.5 MRgFUS for treatment of Parkinson's disease (PICO 3)

Outcome variable: Symptom score

* + No problem
 ? Some problems
 - Major problems

Author, year	Country	Study design	Number of patients	With draws - dropouts	Result MRgFUS Mean (SD) if not otherwise stated	Comments	Directness*	Study limitations*	Precision*
Magara, 2014	Switzerland	Case-series	13	9 (adequate sonications)	Baseline: 39.8 (10.4) 3 months: 15.6 (5.7) p=0.0001*	UPDRS	-	?	-
				4 (inadequate sonications)	Baseline: 36.2 (18.5) 3 months: 33.5 (9.6) p = 0.8042*	UPDRS			
				9 (adequate sonications)	Baseline: 0 3 months: 56.7% (23.0) p=0.0001*	Global symptom relief			
				4 (inadequate sonications)	Baseline: 0 3 months: 22.5% (17.1) p=0.0390*	Global symptom relief			

UPDRS = Unified Parkinson Disease Rating Scale. Max score =147, higher value indicates more severe disease

Global symptom relief is a subjective patient evaluation

*calculated on aggregated data using unpaired Student's t-test (individual data not available), thus underestimating statistical significance.

Appendix 4.6 – Complications

Author, year,	No of participants	Treated condition/disease PICO 1-3	Complications	Comments
Chang, 2015	11	Essential tremor PICO 1	Dizziness, nausea and vomiting in the middle of sonications. Transient mild balance problems.	
Elias, 2013	15	Essential tremor PICO 1	Transient paraesthesias, transient unsteadiness, small first degree burns at pin sites, brief syncopal event.	At 12 months the only serious adverse event was dysesthesia of the index finger.
Jeanmonod, 2012	12	Neuropathic pain PICO 2	Bleeding in the target with ischemia in motor thalamus (n=1). Transient vestibular or vegetative effects.	Finer functions of speaking and writing impeded during demanding interactions after one year.
Lipsman, 2013	4	Essential tremor PICO 1	Paraesthesias in the tips of thumb and index finger. Lower limb deep vein thrombosis.	The thrombosis occurred one week after the procedure. May or may not be related to the immobilization in the MRI scanner.
Magara, 2009	13	Parkinson's disease PICO 3	No post-operative side-effects	

Appendix 5

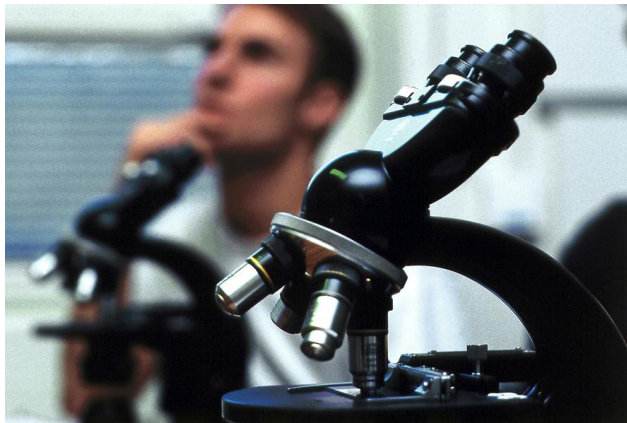
Ethical analysis of Transcranial Magnetic Resonance Guided Focused Ultrasound For Treatment of Essential Tremor, Neuropathic Pain and Parkinson's Disease

Question	Answer/ comment
1. From the patient's perspective, how does this method/technology affect the patient's quality of life and life expectancy?	Improvement of quality of life. No change in life expectancy.
2. How severe is the patient's need that the method/technology must meet?	Essential tremor is a severe social handicap.
3. Does method/technology have any influence on how others view the patient (concerning humanity and human dignity), or on how the patient views himself or herself (concerning humanity and human dignity)?	Not the method itself.
4. Can method/technology affect the patient's ability and possibility to be independent?	Yes, in a favourable way.
5. If implemented, does this method/technology require any special steps to not compromise the patient's autonomy?	No
6. How does this method/technology affect the patient's physical, moral and personal integrity?	No change
7. Is method/technology cost-effective?	The initial cost is very high. Not possible to estimate cost-effectiveness.
8. How does this method/technology affect resources?	See above
9. Is this method/technology in conflict with professional values?	No
10. Does this method/technology change the role of the professional in relation to the patient?	No

11. Does this method/technology affect, or does it put any new demands on, a third party?	No
12. Is there any legislation of relevance with regard to this method/technology?	No
13. Is there any risk of conflict between the procedure of this method/technology and values of the society, or values of different groups?	No
14. Is there a risk that an introduction of this method/technology will cause a conflict with particular interests?	Displacement effects related to the investment costs of the new technology may occur.
15. Can an introduction of the method/technology influence the trust of the health care system?	No
CONCLUSIONS	MRgFUS treatment complies well with most ethical demands. It is less invasive than present methods and less likely to cause complications. The method makes it possible to treat large groups of patients that are excluded from treatment today. In essential tremor and Parkinson's disease it may have a direct effect on ADL functions and quality of life. An ethical problem is the high initial cost of the equipment which is in the range of tens of millions SEK and may have negative implications on other technology investments. The ethical problem is therefore related to possible displacement effects related to the investment costs of a new technology supported by low or very low certainty of evidence for its potential patient benefits and associated risks.

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA



HTA

Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High quality of evidence	= (GRADE ⊕⊕⊕⊕)
Moderate quality of evidence	= (GRADE ⊕⊕⊕⊖)
Low quality of evidence	= (GRADE ⊕⊕⊖⊖)
Very low quality of evidence	= (GRADE ⊕⊖⊖⊖)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh, Professor, MD.
Head of HTA-centrum

