A report for
Universitätsklinikum Schleswig-Holstein/Campus Kiel
on shared decision making
for the treatment of essential tremor

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LIST OF ABBREVIATIONS

AE	Adverse event
B-DBS	Bilateral deep brain stimulation
CADET	Columbia University Assessment of Disability in Essential Tremor
CDSR	Cochrane Database of Systematic Reviews
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CRST	Clinical rating scale for tremor
CTT	Cerebellothalamic tract
DARE	Database of Abstracts of Reviews of Effects
DBS	Deep brain stimulation
ET	Essential tremor
FAQ	Frequently asked question
FTM	Fahn-Tolosa-Marín tremor rating scale
GIN	Guidelines International Network
GK	Gamma knife
HTA	Health technology assessment
IQR	Interquartile range
IQWiG	Institute for Quality and Efficiency in Health Care
IR	Incidence rate
KSR	Kleijnen Systematic Reviews
MA	Meta-analysis
MD	Mean difference
MRgFUS	Magnetic Resonance-Guided Focused Ultrasound thalamotomy
MRI	Magnetic resonance imaging
NA	Not applicable
NE	Not estimable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
OR	Odds ratio
PICOS	Participants, intervention, comparators, outcomes and study design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROS	Prospective analysis
QoL	Quality of life
QUEST	Quality of Life in Essential Tremor
RA	Retrospective analysis
RF	Radiofrequency
RCT	Randomised controlled trial
ROB	Risk of bias
RR	Risk ratio
SDM	Shared decision making
SF-36	Short Form (36) Health Survey
SR	Systematic review
TERAS	The Essential Tremor Rating Scale
U-DBS	Unilateral deep brain stimulation
VIM	Ventral intermediate nucleus

1. PROJECT OBJECTIVE

A key aim of the research project "Making SDM a reality" is to create interactive websites to inform patients as part of shared decision making (SDM).

To support this, Kleijnen Systematic Reviews (KSR) Ltd has prepared an evidence report with a synthesis of the literature underpinning the supporting evidence table of the relevant treatment options.

The topics of this evidence report is the treatment of essential tremor and tremor-dominant Parkinson's disease (PD).

The specific research questions addressed for essential tremor are:

1. What do the treatments* involve?
2. Will my symptoms get better after treatment*?
3. Will my quality of life improve after treatment*?
4. Will I recover after treatment*?
5. What are the risks and the side effects?*
6. Is the treatment* reversible?

* Treatments included: No invasive tremor treatment; deep brain stimulation (DBS); gamma/cyber knife thalamotomy (GK); magnetic resonance-guided focused ultrasound (MRgFUS) thalamotomy

In order to provide some information on the treatment effects to be expected in patients with tremor-dominant PD only results for the comparison of MRgFUS vs. DBS, vs. GK, or no invasive treatment for the effect on tremor were extracted under FAQ-2.

2. METHODS

2.1 INCLUSION CRITERIA

The research question underpinning the literature searches for this topic was developed in conjunction with clinical departments at Universitätsklinikum Schleswig-Holstein/Campus Kiel. The question was framed in terms of participants, intervention, comparators, outcomes and study design (PICOS), see Table 1.

As detailed below, literature searches were carried out using a stepwise approach to identify relevant studies according to study design. In the first step, searches aimed to identify relevant systematic reviews and guidelines.

Table 1: PICOS selection criteria – essential tremor

PICOS	
Patient population	• Adults (40-70 years) with drug resistant/refractory essential tremor
Intervention/Comparators	• No invasive tremor treatment (i.e., no treatment going beyond trying/adding a new medication or medical dose escalation) • Deep brain stimulation (DBS) (unilateral or bilateral) • Gamma knife (GK) thalamotomy (stereotactic radiosurgery) • Magnetic Resonance-Guided Focused Ultrasound (MRgFUS) thalamotomy
Outcomes	• Description of treatment option • Frequency of dosing (where applicable) • Inpatient stay versus outpatient • Resolution of tremor (as measured by any relevant tool, e.g. the Fahn-Tolosa-Marín tremor rating scale [FTM]; the Essential Tremor Rating Assessment Scale [TETRAS]; Columbia University Assessment of Disability in Essential Tremor [CADET], etc.) • Durability of effect over time • Function (as measured by any relevant tool or part of a tool to assess activities of daily living) • Quality of life (as measured by any relevant tool, e.g. measured using the Quality of Life in Essential Tremor [QUEST] questionnaire; the Clinical Rating Scale for Tremor [CRST] Section C, etc.) • Time spent in hospital • Time to return to work • Time to return to normal activities • Time to return to driving • Risks of treatment including complications/adverse effects
Study design	Systematic reviews (SR)/ meta-analyses (MA) (or randomised controlled trials (RCTs), or studies of lower evidence levels (non-randomised/observational studies), if needed.
CADET = Columbia University Assessment of Disability in Essential Tremor; CRST = Clinical Rating Scale for Tremor; FTM = Fahn-Tolosa-Marín tremor rating scale; MA = meta-analysis; MRgFUS = Magnetic Resonance-Guided Focused Ultrasound thalamotomy; QUEST = Quality of Life in Essential Tremor; RCT = randomised controlled trial; SR = systematic review; TETRAS = The Essential Tremor Rating Assessment Scale	

In consultation with the commissioner, questions frequently asked by patients in conjunction with outcomes identified in the literature were developed into an evidence table outline.

In order to provide some information on the treatment effect to be expected in patients with tremor-dominant PD results for the comparison of MRgFUS vs. DBS, vs. GK, or vs. no invasive tremor treatment on the effect on tremor were extracted under FAQ-2.

Table 2: PICOS selection criteria – Parkinson's disease

PICOS	
Patient population	• Adults (40-70 years) tremor-dominant PD
Intervention	• Magnetic Resonance-Guided Focused Ultrasound (MRgFUS) thalamotomy
	• No invasive tremor treatment (i.e., no treatment going beyond trying/adding a new medication or medical dose escalation) • Deep brain stimulation (DBS) (unilateral or bilateral) • Gamma knife (GK) thalamotomy (stereotactic radiosurgery)
Outcomes	• Resolution of tremor (as measured by any relevant tool, e.g. the Fahn-Tolosa-Marín tremor rating scale [FTM]; the Essential Tremor Rating Assessment Scale [TETRAS]; Columbia University Assessment of Disability in Essential Tremor [CADET], etc.) • Durability of effect over time
Study design	Systematic reviews (SR)/ meta-analyses (MA) (or randomised controlled trials (RCTs))
CADET = Columbia University Assessment of Disability in Essential Tremor; CRST = Clinical Rating Scale for Tremor; FTM = Fahn-Tolosa-Marín tremor rating scale; MA = meta-analysis; MRgFUS = Magnetic Resonance-Guided Focused Ultrasound thalamotomy; QUEST = Quality of Life in Essential Tremor; RCT = randomised controlled trial; SR = systematic review; TETRAS = The Essential Tremor Rating Assessment Scale	

2.2 FREQUENTLY ASKED QUESTIONS

Table 2 shows the identified – and slightly reorganised – research questions (frequently asked questions; FAQs) with relevant outcomes.

Table 3: Frequently asked questions and related outcomes

FAQ 1: What does the treatment involve?
• What happens to me during the treatment? • Where will the treatment take place? • Will I need an anaesthetic? • How long might I be in hospital? • Will I have to go back into hospital? • Is the treatment reversible?
FAQ 2: Will my symptoms get better?
• Will my tremor improve?[a] • Will the function of my limbs improve?
FAQ 3: What will be the impact on my daily living?
• Will I be able to return to my usual activities? • Will I be able to return to work? • Will I be able to drive/return to driving? • Will my quality of life improve?
FAQ 4: What are the possible adverse effects of treatment?
• What side effects might I experience from my treatment? • What risks are associated with treatment?
FAQ = frequently asked question [a] Also for tremor-dominant PD

2.3 LITERATURE SEARCHES

Literature searches were conducted to identify systematic reviews and guidelines about essential tremor and tremor in Parkinson's disease.

The search strategies were developed specifically for each database and the keywords adapted according to the configuration of each database. Searches were limited by date range for systematic reviews and guidelines to 2012-2019. Searches were not limited by language or publication status.

Systematic reviews and guidelines

The following systematic review specific databases were searched from 2012:

- Cochrane Database of Systematic Reviews (CDSR) (Wiley): Issue 10 of 12, October 2019
- Database of Abstracts of Reviews of Effects (DARE) (CRD): 2012 to 31 Mar 2015
- Health Technology Assessment (HTA) database (CRD): 2012 to 31 Mar 2018
- KSR Evidence (Internet) (https://ksrevidence.com/): 2012-2019/10/10
- Epistemonikos (Internet) (https://www.epistemonikos.org/): 2012-2019/10/10

The following guidelines resources were searched from 2012:

- Guidelines International Network (GIN) (Internet) (https://www.g-i-n.net/home): up to 2019/10/15
- NICE Evidence (Internet) (www.evidence.nhs.uk/): 2012-2019/10/15
- NICE Guidance (Internet) (https://www.nice.org.uk/guidance): 2012-2019/10/15
- ECRI Guidelines Trust (Internet) (https://guidelines.ecri.org/): 2012-2019/10/15

Full details of all search strategies are presented in Appendix 1.

Handling of citations

Identified references from the bibliographic database searches were downloaded into EndNote bibliographic management software for further assessment and handling.

Supplementary searches

Reviewers also conducted internet searches to identify other potentially relevant references, e.g. guidance specific to Germany and websites of patient organisations.

2.4 METHODS OF STUDY SELECTION AND DATA EXTRACTION

Study selection

Two reviewers independently screened the title and abstract of each record identified by the search to determine its likely relevance to the review. Due to the large number of potentially relevant records, prioritisation criteria (i.e. publication date ≥ 2014) were established and full papers were obtained for the prioritised references, independently checked, and inclusion criteria applied. Any disagreements were resolved through discussion.

Data extraction

An evidence hierarchy was used to select the most appropriate study(ies) to populate the evidence table. Where more than one study could provide evidence for the table the most relevant studies were extracted using the following criteria: recency (most recent preferred), quality (highest quality preferred), representativeness (populations representative of the general target population preferred). Where there were gaps in the evidence table (no systematic review or guideline available) relevant RCTs were extracted and where no RCTs were available observational studies were extracted. For each study, data were extracted by one reviewer and checked by another. Any

disagreements were resolved by consensus. Only data from studies that reported on at least two interventions of interest were extracted for this report unless they had been pooled in the systematic review that was used as a source, i.e. single case series were not extracted. For PD only evidence based on RCTs was extracted.

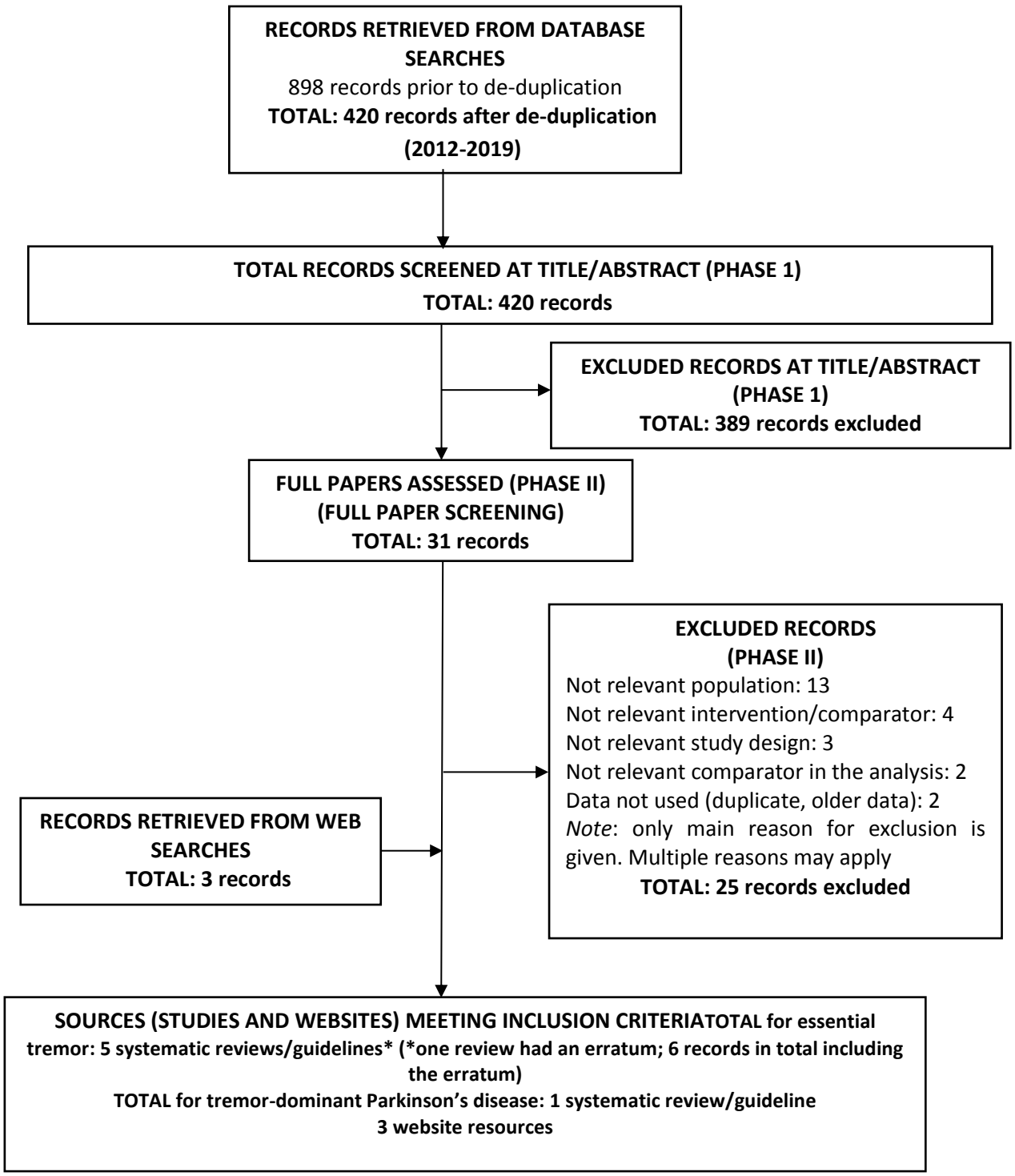
3. RESULTS

3.1 LITERATURE SEARCH RESULTS AND INCLUSION ASSESSMENT

A total of 898 records were retrieved from literature searches. After de-duplication, 420 titles and abstracts (published between 2012 and 2019) were screened by two reviewers. Of these, 31 full papers were identified as potentially relevant. After further review, seven records reporting on six systematic reviews/guidelines (including one erratum) were selected for inclusion in this report. In addition, two websites with patient information were used to describe the different treatment interventions (i.e. FAQ 1).

A summary of the study selection process according to a modified PRISMA flow chart is reported in Figure 1 and a description of the included studies in Table 3.

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study flow diagram



3.2 OVERVIEW OF THE EVIDENCE

The information identified to answer the four FAQs is summarised in Table 4 organised by question. In order to increase clarity, the table only describes the interventions and comparators of interest for this report even though some of the systematic reviews also investigated other comparisons or outcomes.

Table 4: Summary of evidence sources

Study	Evidence type	Intervention	Comparators	What does the treatment involve?	How might I feel after my treatment?	What will be the impact on my daily living?	What are the side effects of treatment?
Essential tremor – Guidelines, systematic reviews and meta-analyses							
Health Quality Ontario HTA 2018[1]	HTA (SR)	MRgFUS	Sham, DBS, U-DBS, B-DBS	✓	✓	✓	✓
Schreglmann 2018[2]	SR and MA	MRgFUS, GK	Baseline	-	✓	-	✓
Langford 2018[3]	SR	MRgFUS	U-DBS	-	✓	✓	-
Mohammed 2018[4 5]	MA	MRgFUS	Baseline	-	✓	✓	✓
NICE IPG6172018[6]	SR	MRgFUS	Sham, U-DBS, B-DBS	✓	✓	✓	-
Tremor-dominant Parkinson's disease – Guidelines, systematic reviews and meta-analyses							
NICE IPG606 2018 [7]	SR	MRgFUS	Sham		✓		
Websites – patient information							
National Tremor Foundation[8]	Patient information	No invasive treatment (medication); DBS	NA	✓	-	-	-
International Essential Tremor Foundation[9]	Patient information	DBS, MRgFUS, GK	NA	✓	-	-	-
Parkinsons UK[10]	Patient information	No invasive treatment	NA	✓			

B-DBS = bilateral deep brain stimulation; DBS = deep brain stimulation; GK = gamma knife; HTA = Health technology assessment; MA = meta-analysis; MRgFUS = Magnetic Resonance-Guided Focused Ultrasound thalamotomy; NA = not applicable; SR = systematic review; STC simulated treatment comparison; U-DBS = unilateral deep brain stimulation

FAQ 1: WHAT DOES THE TREATMENT INVOLVE?

This section covers the rationale for the treatment of essential tremor including the eligibility for treatment, and a description of the different surgical procedures with respect to the following questions:

- What happens to me during the treatment?
- Where will the treatment take place?
- Will I need an anaesthetic?
- How long might I be in hospital?
- Will I have to go back into hospital?
- Is the treatment reversible?

This information is summarised in Table 5 and taken from two studies and two websites reporting patient information.

Table 5: Description of treatments

Treatment options for ET[1, 7, 9, 10]
Essential tremor is an uncontrollable shake or tremble which affects part of the body, most commonly experienced as a trembling up and down of the hands or limbs during movement, but that can also affect other parts of the body including the arms, head, eyelids, lip and even the larynx (causing a shaky voice) when at rest. The tremor is usually most noticeable when you try to hold still or do something with your hands such as write. The tremor usually becomes more severe over time. Typically, tremor in PD occurs at rest, i.e. when you are still and relaxed, and becomes less marked with voluntary movement but you can also have action tremor. Usually, the tremor in PD starts in the distal upper limb - a typical form of tremor here is the "pill-rolling" rest tremor of the hand - and affects other parts of the body at later stages. The tremor can start in other parts of the body than the hand though. In tremor-dominant PD the tremor is the main symptom requiring treatment. There is no cure for essential tremor or tremor due to PD, but treatments can help patients manage their symptoms. Drugs are usually the first treatments to be used. However, unfortunately around 50% of patients with essential tremor will experience recurrent tremor or inadequate tremor control while taking medications. For these patients with medication-refractory tremor (people who have not responded adequately to best medical therapy) surgical options may be considered. Surgical treatments include: DBS, GK and magnetic resonance-guided focused ultrasound thalamotomy. In order to alleviate tremor in a patient's right arm, surgery is performed on the left side of the brain and vice versa for the left arm.
Non-invasive tremor treatment of ET[7, 9]
Am I eligible for treatment? Each drug has its own eligibility criteria. *What happens to me during the treatment?* The first treatment option for many patients with essential tremor is usually pharmacotherapy either intermittent or continuous treatment. This commonly includes medications like the beta-blocker propranolol and the anticonvulsant primidone or benzodiazepines (clonazepam) for high stress

situations. Options for continuous treatment can include: propranolol; primidone; topiramate; gabapentin; clonazepam; atenolol; sotal; clonazepam; nadolol; and diazepam.

Where will the treatment take place?
At home.

Will I need an anaesthetic?
No.

How long might I be in hospital?
Hospital stay not required.

Will I have to go back into hospital?
Only to attend regular check-up/monitoring appointments if needed/as required.

Is the treatment reversible?
Yes.

Non-invasive treatment tremor in PD[7, 10]

Am I eligible for treatment?
Each drug has its own eligibility criteria.

What happens to me during the treatment?
Treatment of PD such as levodopa and some dopamine agonists can also help with the tremor as well as other drugs. Some patients find that squeezing or rolling a ball or other object can help in the early stages.

Where will the treatment take place?
At home.

Will I need an anaesthetic?
No.

How long might I be in hospital?
Hospital stay not required unless the drugs are supplied via pumps.

Will I have to go back into hospital?
Only to attend regular check-up/monitoring appointments if needed/as required.

Is the treatment reversible?
Yes.

Deep brain stimulation (DBS)[8, 9]

Am I eligible for treatment?
Considered in people whose condition has not responded adequately to best medical therapy. Patients with dementia and/or other illnesses like depression, medically induced hallucinations, significant memory problems or psychosis, are not eligible for DBS. DBS may also not be suitable for older patients due to the potential risks of adverse events. The same applies to patients with other medical conditions that may increase the risks associated with brain surgery or to patients with short expected life spans.

What happens to me during the treatment?
This is one of the main types of surgery used to treat essential tremor and is a non-destructive

surgery, meaning no part of the brain is destroyed. This method usually involves: series of brain scans to the patient's skull and implantation of fine, electrode-tipped wires into the brain through a small hole (around 2cm in diameter) on the top of the head. It can vary whether a frame is used or not. The wires are connected to extensions located under the skin behind the ear and down the neck towards a pulse generator, which is placed under the skin in the chest. The purpose is to deliver high frequency stimulations to a specific part of the brain. These stimulations interfere with the electrical signals of the brain that cause essential tremor. The surgery can be applied to one (unilateral) or both (bilateral) sides of the brain. For bilateral DBS the electrodes will be passed through separate holes in the skull but will be attached via a wire to the same generator.

Where will the treatment take place?
In hospital operating theatre.

Will I need an anaesthetic?
The wires are usually implanted whilst the patient is awake. This allows the surgeon to check with the patient whether the placement of the electrodes is correct by asking him about any potential side-effects and whether his symptoms have improved. The patient's skin receives a local anaesthetic so that they do not feel pain. The brain does not feel pain as it does not contain any pain receptors.

How long might I be in hospital?
Patients are usually admitted for further tests, one to three days before surgery. The length of the operation depends on the technique used, but often lasts between three to six hours from start to finish. After DBS, patients are usually briefly transferred to a recovery ward for a period of observation before being transferred onto a neurosurgical or neurological ward. The amount of time needed in hospital depends on the centre implanting the device. If the electrodes are accurately placed, without complications, the recovery period usually lasts from between three to five days, after which the patient is discharged.

Will I have to go back into hospital?
Usually a series of planned outpatient appointments are required. Other unscheduled hospital stays may be necessary if there are complications or adjustments need to be made to the electrical stimulations to reduce adverse effects or maximise tremor control. The battery will also need replacing every three to seven years depending on the stimulation settings used (outpatient procedure).

Is the treatment reversible?
Can be reversible and if the surgery is unsuccessful the system can be switched off and/or removed.

GK (gamma knife, stereotactic radiosurgery)[9]

Am I eligible for treatment?
Considered in people whose condition has not responded adequately to best medical therapy. Patients with dementia and/or other illnesses like depression, medically induced hallucinations, significant memory problems or psychosis, are not good candidates for GK surgery as these conditions may increase the risk of adverse events. The same applies to patients with other medical conditions that may increase the risks associated with brain surgery or to patients with short expected life spans. GK (radiosurgical thalamotomy) is less commonly used as a surgical treatment for ET but is a treatment option for patients who cannot undergo DBS.

What happens to me during the treatment?

This procedure is performed noninvasively by focusing radiation beams through the skull to a particular part of the brain to destroy the tissue and so interrupt the signals in the brain causing the ET. To identify the target area in the brain several imaging techniques can be used and a metal frame (stereotactic frame) will be fixed to the head in order to help accurately guide the radiation beams. Unlike the other types of surgery, it is not possible to test that the radiation beams have identified the correct target location during the surgery. The effects of the procedure, in terms of both tremor control and adverse effects, do not appear until weeks or months after the radiosurgery. Usually one side of the brain is treated initially (unilateral) and then after further assessment the procedure can be performed on the other side of the brain.

Where will the treatment take place?

In hospital operating theatre.

Will I need an anaesthetic?

The procedure is not painful and no cuts are made into the skin/skull, but a local anaesthetic is used to numb the skin around the areas of the scalp and forehead where the stereotactic frame is attached.

How long might I be in hospital?

The procedure may be performed as an outpatient procedure. The length of the procedure depends on the individual hospital but is usually around an hour. After the head frame is removed patients are usually allowed home.

Will I have to go back into hospital?

Planned outpatient appointments may be required to follow-up after the procedure. Other unscheduled hospital stays may be necessary if there are complications.

Is the treatment reversible?

No.

Magnetic Resonance-Guided Focused Ultrasound thalamotomy (MRgFUS)[1, 7, 9]

Am I eligible for treatment?

Considered in people whose condition has not responded adequately to best medical therapy. Patients with dementia and/or other illnesses like depression, medically induced hallucinations, significant memory problems or psychosis, are not eligible for MRgFUS. The same applies to patients with other medical conditions that may increase the risks associated with brain surgery or to patients with short expected life spans.

What happens to me during the treatment?

MRgFUS is similar to GK, but instead of using radiation waves it uses ultrasound waves to destroy a small area of brain tissue (procedure is transcranial and involves no incision or drilling) so interrupting the signals in the brain causing the ET. Before the procedure, a stereotactic head frame is attached the patients head to guide the ultrasound beams (similar to the GK surgery). After that, the whole procedure is carried out whilst the patient is lying down inside an MRI scanner. Unlike GK surgery it is possible during MRgFUS, to use MRI and thermal imaging to identify the exact target area of the brain and monitor the treatment as it happens. When the chosen area of the brain is confirmed, high-power ultrasound (sound wave) pulses are focussed on the target area of the brain, which then heats up destroying the surrounding brain tissue. Unfortunately, unlike DBS, MRgFUS can

only be done on one side of the brain (unilateral) because of the high incidence of adverse effects with bilateral lesions.

Where will the treatment take place?
In hospital operating theatre.

Will I need an anaesthetic?
Patients are kept awake so they can report any improvement or adverse events to the operator during the procedure. Since this procedure does not involve incision or drilling, no anaesthesia is required.

How long might I be in hospital?
The duration of the procedure is about three hours and symptom relief should be immediate. Recovery time is generally shorter than for some other treatments.

Will I have to go back into hospital?
Planned outpatient appointments may be required to follow-up after the procedure. Other unscheduled hospital stays may be necessary if there are complications.

Is the treatment reversible?
No.

DBS = deep brain stimulation; ET = essential tremor; GK = gamma knife; MRgFUS = Magnetic Resonance-Guided Focused Ultrasound thalamotomy; MRI = magnetic resonance imaging

FAQ 1: EVIDENCE SUMMARY

What does treatment involve?

Pharmacological treatment of essential tremor usually involves propranolol or primidone, depending on the patient's medical conditions and potential side effects. Treatment may be intermittent (when needed, e.g. for high stress situations) or continuous. Further options for continuous treatment include: topiramate; gabapentin; clonazepam; atenolol; sotalol; clonazepam; nadolol; and diazepam.

Pharmacological treatment of Parkinsons disease can improve the symptoms of tremor as well when drugs such as levodopa and some of the dopamine agonists are used.

If patients with ET or PD are or become refractory to pharmacological treatment then for these patients surgical options may be considered.

The two main options for **neurosurgical treatment** are lesional surgery (magnetic resonance-guided focused ultrasound – MRgFUS or gamma knife – GK) and deep brain stimulation (DBS). DBS involves implanting permanent electrodes into the affected brain areas. This is a reversible and adjustable procedure that can be performed on one (unilateral) or both (bilateral) sides of the brain. In comparison, lesional surgery (thalamotomy) involves destroying part of the brain tissue responsible for causing the tremor, but without making incisions in the scalp and brain tissue. This is irreversible and can involve the use of ultrasound waves (MRgFUS) or radiation (GK). Unlike DBS, MRgFUS and GK are types of lesional surgery and can only be performed unilaterally. GK may be performed on the other side of the brain at a later date after a period of recovery and assessment but unlike MRgFUS it does not allow to test during the procedure whether the right target area has been identified. Both lesional surgery and DBS can alleviate tremor, but there are risks involved with each procedure.

FAQ 2: WILL MY SYMPTOMS GET BETTER?

Results are presented by outcome in the following tables. For each outcome the column "intervention favoured" just describes the direct of the effect not whether the effect was significant or how good the quality of the evidence is. Where available, this information is provided in the columns with the effect estimates and for the quality of the evidence.

Will my tremor improve? Will the function of my limbs improve?

In the included studies tremor severity was assessed using the Clinical Rating Scale for Tremor (CRST) which assesses various aspects of tremor severity. For evidence on tremor abolition, tremor recurrence, and tremor severity/function see Tables 6 to 9. The CRST scale is an adapted version of the Fahn–Tolosa–Marín (FTM) Clinical Rating Scale for Tremor and comprises three subscales covering different aspects of tremor including: part A (action tremor); part B (tasks of writing, drawing and pouring); and part C (functional disability/activities of daily living).[1] The maximum possible score is 152 and higher scores indicate greater tremor severity.

In addition, to using CRST scores, one study (Kim 2017 reported in Health Quality Ontario HTA 2018[1]) used tremor abolition and >90% abolition as outcomes. This study (Kim 2017 reported in Health Quality Ontario HTA 2018[1]) also assessed the re-occurrence of tremor.

Limb function was assessed using various rating scores and in particular the CRST part B, which particularly focuses on limb tremor and its effects on movement.

The two FAQs are being presented together as: 1. The severity of the tremor is likely to affect the function of the limbs and 2. The rating scales tend to contain sections that measure the severity of the tremor, the performance when specific tasks need to be accomplished, and function. Any allocation of these outcomes to one FAQ or the other therefore seemed arbitrary in most instances.

No invasive tremor treatment

No evidence.

DBS

See MRgFUS versus DBS

Gamma/cyber knife thalamotomy

See MRgFUS versus GK below.

MRgFUS

Pooled data were available from one systematic review (Mohammed 2018[4, 5]). This review pooled eight studies mainly comprising evidence from lower level studies (five retrospective and two prospective observational studies); only one of the eight studies used a randomised design. Pooled values suggested that the mean improvement in total CRST score (i.e. improvement in tremor severity) in MRgFUS treated patients in comparison to baseline (pre-treatment) was 62.2% (46.0% to 76.0%), but heterogeneity was moderate (I^2=61.0%). The review authors overall concluded that MRgFUS therapy significantly improves essential tremor.

The remaining evidence was reported by two systematic reviews[1, 6] and focused on the findings of one RCT by Elias 2016 (data taken from Health Quality Ontario HTA 2018[1]) that compared MRgFUS to a sham procedure. The study was rated as high quality in both reviews and assessed overall tremor severity using the CRST tool at baseline, three months and 12 months. Those in the MRgFUS group appeared to experience a much greater improvement (41% versus 2%) in overall CRST score and in upper limb tremor severity using CRST parts A and B (see Table 8) compared with sham treatment. The improvement was sustained at one year, though no comparison between treatments could be made due to almost all patients (19 out of 20) in the sham group crossing over to the MRgFUS treatment group after three months.

The two systematic reviews reporting on this study both concluded that MRgFUS was effective at reducing essential tremor.

MRgFUS versus DBS

One retrospective observational study (Kim 2017 included in a systematic review by Health Quality Ontario HTA 2018[1]) reported on the number (percentage) of patients achieving the complete abolition of tremor and tremor abolition in terms of the number (percentage) of patients with >90% improvement in tremor. This study was assessed as providing only very low quality evidence and only descriptively compared the proportions in the two arms. The study suggested that after one month and after 12 months proportions of patients achieving >90% improvement were similar for those treated with MRgFUS compared to DBS (see Table 8). Levels of tremor recurrence were also similarly low (4%-5%) after one month (see Table 7).

Two further observational studies (Huss 2016 and Blomstedt 2007; data taken from Health Quality Ontario HTA 2018[1]), one of which was rated as very low evidence (Huss 2016; data taken from Health Quality Ontario HTA 2018[1]), were also included in the systematic reviews.[1, 3] Both of these studies suggested that the overall CRST scores tended to favour DBS over MRgFUS (see Table 8), but the evidence is very low quality

The NICE IPG617 assessment of MRgFUS[6] reported on very low level evidence from one retrospective observational study (Huss 2015; data taken from NICE IPG617[6]) that assessed MRgFUS and bilateral/unilateral DBS. Both interventions showed CRST scores in in the treated hand (or right hand if treatment was bilateral) were similar.

MRgFUS versus GK

Schreglmann 2018[2] reported on pooled values for the change in upper limb tremor severity using standardised mean difference (Hedge's g) and comparing MRgFUS with GK. The studies included in the review used various different validated scales to measure tremor and Hedge's g allows these to be all combined in one pooled value by transforming the original data into one uniform scale. A negative effect size indicates improvement of tremor. The review reported pooled values for MRgFUS (separately pooled for the CTT [cerebellothalamic tract] and vim [ventral intermediate nucleus]) and GK (vim). The effect on upper limb tremor severity appeared similar across the different intervention groups (see Table 8), but moderate to high levels of heterogeneity were reported for the pooled values for MRgFUS (vim) and GK (vim).

Table 6: Summary of evidence on tremor abolition

Outcome	Author	No. of studies (type of study)	Average follow up time (years)	Intervention Percentage (95% CI)	Comparator Percentage (95% CI)	Mean difference, points (95% CI)	Intervention favoured (direction of the effect)	Quality of evidence (GRADE)
Systematic reviews with pooled effect sizes – 1st level evidence								
No evidence								
RCTs – 2nd level evidence								
No evidence								
Observational studies – 3rd level evidence								
Complete tremor abolition	Health Quality Ontario HTA 2018[1] (Kim 2017)[11]	1 (RA)	1 month	**MRgFUS** 43.5% (23.2 to 63.8%)	**DBS** 31.6% (10.7 to 52.5%)	NR	MRgFUS	VERY LOW
Complete tremor abolition	Health Quality Ontario HTA 2018[1] (Kim 2017) [11]	1 (RA)	1	**MRgFUS** 34.8% (15.3 to 54.2%)	**DBS** 47.4% (24.9 to 69.9%)	NR	DBS	VERY LOW

B-DBS = bilateral deep brain stimulation; CI = confidence interval; CRST = clinical rating scale for tremor; CTT = cerebellothalamic tract; DBS = deep brain stimulation; GK = gamma knife; IQR = interquartile range; MIB = mean improvement vs. baseline; MRgFUS = Magnetic Resonance-Guided Focused Ultrasound thalamotomy; NA = not applicable; NR = not reported; PROS = prospective analysis; RA = retrospective analysis U-DBS = unilateral deep brain stimulation; vim = ventral intermediate nucleus

Table 7: Summary of evidence on tremor recurrence

Outcome	Author	No of studies (type of study)	Average follow up time (years)	Intervention Number of patients	Comparator Number of patients	Intervention favoured (direction of the effect)	Quality of evidence (GRADE)
Systematic reviews with pooled effect sizes – 1st level evidence							
No evidence							
RCTs – 2nd level evidence							
No evidence							
Observational studies – 3rd level evidence							
Return to baseline tremor severity	Health Quality Ontario HTA 2018[1] (Kim 2017) [11]	1(RA)	1	**MRgFUS** 1 (4.3%)	**DBS** 1 (5.2%)	NR	VERY LOW

Outcome	Author	No of studies (type of study)	Average follow up time (years)	Intervention Number of patients	Comparator Number of patients	Intervention favoured (direction of the effect)	Quality of evidence (GRADE)
DBS = deep brain stimulation; MRgFUS = Magnetic Resonance-Guided Focused Ultrasound thalamotomy; NR = not reported; RA = retrospective analysis; RCT = randomised controlled trial							

Table 8: Summary of evidence on tremor severity for essential tremor

Outcome	Author	No. of studies (type of study)	Average follow up time (years)	Intervention Mean score (SD)	Comparator Mean score (SD)	Mean difference, points (95% CI)	Intervention favoured (direction of the effect)	Quality of evidence (GRADE)
Systematic reviews with pooled effect sizes – 1st level evidence								
Overall tremor severity (total CRST score)[c]	Mohammed 2018[4]	8 (1RCT, 5RA and 2PROS)[12-19]	NR	**MRgFUS**	**Baseline**	62.2% (46.0% to 76.0%); I^2=61.0%	MRgFUS	NR
Change in upper limb tremor severity	Schreglmann 2018[2]	2 (NR)	NR	**MRgFUS CTT**	**Baseline (i.e. pre-treatment)**	-2.35 (-2.51 to -2.19)[f]; I^2=0%	MRgFUS	NR
Change in upper limb tremor severity	Schreglmann 2018[2]	3 (NR)	NR	**MRgFUS vim**	**Baseline (i.e. pre-treatment)**	-2.08 (-2.77 to -1.39)[f]; I^2=51%	MRgFUS	NR
Change in upper limb tremor severity	Schreglmann 2018[2]	6 (cohorts)	NR	**GK vim**	**Baseline (i.e. pre-treatment)**	-2.13 (-3.78 to -0.48)[f]; I^2=92%	GK	NR
RCTs – 2nd level evidence								
Overall tremor severity (total CRST score)[c]	Elias 2016 [15] reported in two SR[1, 6]	1 (RCT)	Baseline	**MRgFUS** 50.1 (14.0)	**Sham** 44.1 (12.7)	NA	NA	NR
		1 (RCT)	3 months	**MRgFUS** 29.6 (13.0) MIB = 41%	**Sham** 43.1 (13.1) MIB = 2%	-13.50 (-20.17 to -6.83)	MRgFUS	HIGH
		1 (RCT)	1	**MRgFUS** 32.4 (14.5)	NR	NR	NR	HIGH

Outcome	Author	No. of studies (type of study)	Average follow up time (years)	Intervention Mean score (SD)	Comparator Mean score (SD)	Mean difference, points (95% CI)	Intervention favoured (direction of the effect)	Quality of evidence (GRADE)
				MIB = 35%				
Upper extremity tremor severity (CRST parts A and B)[b]	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	Baseline	**MRgFUS** 18.1 (4.8)	**Sham** 16.0 (4.4)	NA	NR	NR
		1 (RCT)	3 months	**MRgFUS** 9.6 (5.1) MIB = 47%	**Sham** 15.8 (4.9) MIB = 0.1%	-8.3 (-5.9 to -10.7)[a]	MRgFUS	HIGH
		1 (RCT)	1	**MRgFUS** 10.9 (4.5) MIB = 40%[d]	NR	NR	NR	HIGH
Observational studies – 3rd level evidence								
Overall tremor severity (total CRST score)[c]	Health Quality Ontario HTA 2018[1] (Huss 2016)[17]	1 (RA)	MRgFUS (1) B-DBS (13 months) U-DBS (9 months)	**MRgFUS** 17.7 (NR) MIB = 55.7%[d]	**B-DBS** 13.2 (NR) MIB = 79.5%[d] **U-DBS** 15.8 (NR) MIB = 62.8%[d]	NR MRgFUS vs B-DBS: p<0.05 U-DBS vs B-DBS: p<0.05	B-DBS	VERY LOW
	Langford 2018[3] (Blomstedt 2007)[20]	1 (PROS)	1	**MRgFUS**	**U-DBS**	0.21 (-9.32 to 9.74)	MRgFUS	NR
Tremor improvement[e]	Health Quality Ontario HTA 2018[1] (Kim 2017)[11]	1 (RA)	1 month	**MRgFUS** >90% improvement in 91.3% of patients (95% CI 79.8 to 100%)	**DBS** >90% improvement in 89.5% of patients (95% CI 75.7 to 100%)	NR	MRgFUS	VERY LOW
Tremor improvement[e]	Health Quality Ontario HTA 2018[1] (Kim	1 (RA)	1	**MRgFUS** >90% improvemen	**DBS** >90% improvement	NR	DBS	VERY LOW

Outcome	Author	No. of studies (type of study)	Average follow up time (years)	Intervention Mean score (SD)	Comparator Mean score (SD)	Mean difference, points (95% CI)	Intervention favoured (direction of the effect)	Quality of evidence (GRADE)
	2017)[11]			t in 78.3% of patients (95% CI 66.8 to 89.8%)	in 84.2% of patients (95% CI 67.8 to 100%)			
CRST score in treated hand (right if bilateral)	NICE IPG617[6] (Huss 2015) [17]	1 (RA)	MRgFUS (1) B-DBS (13 months) U-DBS (9 months)	**MRgFUS** 5.7 (NR) MIB = 74.5%[d]	**B-DBS** 5.2 (NR) 74.5%[d] **U-DBS** 5.6 (NR) 78.9%[d]	NR	U-DBS	NR
Hand tremor severity (CRST score Part A)	NICE IPG617[6] (Huss 2015) [17]	1 (RA)	MRgFUS (1) B-DBS (13 months) U-DBS (9 months)	**MRgFUS** 8.7 (NR) MIB = 35.1%[d]	**B-DBS** 3.8 (NR) MIB = 82.8%[d] **U-DBS** 8.4 (NR) MIB = 56.0%[d]	NR MRgFUS vs B-DBS: p<0.05 U-DBS vs B-DBS: p<0.05	B-DBS	NR
CRST score Part B, tasks	NICE IPG617[6] (Huss 2015) [17]	1 (RA)	MRgFUS (1) B-DBS (13 months) U-DBS (9 months)	**MRgFUS** 12.7 (NR) MIB = 46.2%[d]	**B-DBS** 7.1 (NR) MIB = 68.3%[d] **U-DBS** 10.2 (NR) MIB = 52.6%[d]	NR MRgFUS vs B-DBS: p<0.05 U-DBS vs B-DBS: p<0.012	B-DBS	NR

[a] The between group difference in the mean change at 3 months;

[b] Upper extremity tremor severity was assessed via parts A and B of the Clinical Rating Scale for Tremors (CRST), where higher scores indicate greater severity. The maximum possible score is 32;

[c] Overall tremor severity was assessed via parts A, B, and C of the Clinical Rating Scale for Tremors (CRST), where higher scores indicate greater tremor severity. The maximum possible score is 152.

[d] Corresponds to statistically significant difference from baseline (p<0.05) [e] The authors categorised > 90% improvement as occasional tremor

[f] Standardised mean difference (Hedge's g) - transforms original data from various validated tremor scales into a uniform scale and allows data to be combined from studies using

Outcome	Author	No. of studies (type of study)	Average follow up time (years)	Intervention Mean score (SD)	Comparator Mean score (SD)	Mean difference, points (95% CI)	Intervention favoured (direction of the effect)	Quality of evidence (GRADE)
different scales and subscales B-DBS = bilateral deep brain stimulation; CI = confidence interval; CRST = clinical rating scale for tremor; CTT = cerebellothalamic tract; DBS = deep brain stimulation; GK = gamma knife; IQR = interquartile range; MIB = mean improvement vs. baseline; MRgFUS = Magnetic Resonance-Guided Focused Ultrasound thalamotomy; NA = not applicable; NR = not reported; PROS = prospective analysis; RA = retrospective analysis; RCT = randomised controlled trial; SR = systematic review; U-DBS = unilateral deep brain stimulation; vim = ventral intermediate nucleus								

Table 9: Summary of evidence on tremor severity for tremor-dominant Parkinson's disease

Outcome	Author	No. of studies (type of study)	Average follow up time (years)	Intervention Mean score (SD)	Comparator Mean score (SD)	Mean difference, points (95% CI)	Intervention favoured (direction of the effect)	Quality of evidence (GRADE)
Systematic reviews with pooled effect sizes – 1st level evidence								
No evidence								
RCTs – 2nd level evidence								
Tremor subscore (CRST A+B), treated hand	NICE IPG606 [7] (Bond 2017, USA)[21]	1 (RCT)	Baseline	**MRgFUS** 17 points (n=20)	**Sham** 23 points (n=7)	NA	NA[a]	NA
Tremor subscore (CRST A+B), treated hand (improvement from baseline)	NICE IPG606 [7] (Bond 2017, USA)[21]	1 (RCT)	3 months	**MRgFUS** Median: 7 (IQR:3.5 to 14.0) points Median: 62% (IQR: 22.0 to 79.0)	**Sham** Median: 2 (IQR: 3.0 to 6.0) points Median: 22% (IQR: -11.0 to 29.0)	NR p=0.04	MRgFUS	NR
CRST total	NICE IPG606 [7] (Bond 2017,	1 (RCT)	3 months	**MRgFUS** Median: 18	**Sham** Median: 3	NR	MRgFUS	NR

Outcome	Author	No. of studies (type of study)	Average follow up time (years)	Intervention Mean score (SD)	Comparator Mean score (SD)	Mean difference, points (95% CI)	Intervention favoured (direction of the effect)	Quality of evidence (GRADE)
	USA)[21]			(IQR: 12.0 to 25.0) Median: 44% (IQR: 23.0 to 78.0)	(IQR: - 4.0 to 17.0) Median: 12% (IQR: -8.0 to 37.0)			
Resting tremor (item 20), treated hand[b]	NICE IPG606 [7] (Bond 2017, USA)[21]	1 (RCT)	3 months	**MRgFUS** Median: 1.5 (IQR: 0 to 3.0)	**Sham** Median: 0 (IQR: 0 to 0)	NR	MRgFUS	NR
Postural or action tremor (item 21), treated hand[b]	NICE IPG606 [7] (Bond 2017, USA)[21]	1 (RCT)	3 months	**MRgFUS** Median: 1 (IQR: 0.5 to 2.5)	**Sham** Median: 0 (IQR: 0 to 2.0)	NR	MRgFUS	NR
Observational studies – 3rd level evidence								
No evidence								

[a] Baseline points before intervention

[b] Assessed using UPDRS

CRST = clinical rating scale for tremor; IQR = interquartile range; MRgFUS = Magnetic Resonance-Guided Focused Ultrasound thalamotomy; NA = not applicable; NR = not reported; RCT = randomised controlled trial; SR = systematic review;

FAQ 2: EVIDENCE SUMMARY

Will my symptoms get better?

Essential tremor

Tremor abolition/recurrence

Evidence from one very low quality retrospective study suggested that the proportions of patients experiencing complete abolition of tremor at one month and one year were similar between those treated with MRgFUS and those treated with DBS (30% to 40%).

Tremor severity

One RCT comparing MRgFUS with sham found that patients who had undergone MRgFUS thalamotomy reported improved treatment effects in upper extremity tremor and overall tremor severity compared to patients in the sham group.

Evidence from one high quality RCT (reported in two systematic reviews) and one pooled analysis of lower quality observational studies suggested that MRgFUS imported overall tremor and upper tremor severity when compared with baseline.

Very low quality evidence from two retrospective observational study suggested that bilateral DBS improved overall tremor and hand tremor more so than MRgFUS or unilateral DBS.

One systematic review suggested an improvement in upper level limb tremor severity from baseline for patients treated with MRgFUS and GK and that improvement appeared similar across the different treatments. However, there appeared to be moderate to high levels of heterogeneity between the studies which mainly appeared to be observational studies. In comparison, one retrospective observational study suggested similar improvements in hand tremor severity for MRgFUS and DBS patients.

Tremor recurrence

One very low quality retrospective study reported that after one year of follow-up levels of tremor recurrence were low, with one patient returning to baseline tremor severity in each of two treatment groups (MRgFUS and DBS).

Tremor-dominant Parkinson's disease

Tremor severity

One RCT comparing MRgFUS with sham found that patients who had undergone MRgFUS thalamotomy reported improved treatment effects in resting and postural or action tremor. The tremor subscore (CRST A +B) of the treated hand was also statistically significantly improved in the treatment group when compared with the sham group.

FAQ 3: WHAT WILL BE THE IMPACT ON MY DAILY LIVING?

FAQ 3a: Will I be able to return to my usual activities?

Functional abilities were assessed using part C of the CRST questionnaire in the included studies (see Table 10). This consists of eight items, each of which is scored between 0 to 4 (i.e. total part C score ranges from 0 to 32). Part C assesses functional disability in activities of daily living, i.e. disabilities affecting speaking, eating, drinking, hygiene, dressing, writing, and working. Higher scores equate to more severe disability.

No invasive tremor treatment

No evidence.

DBS

See MRgFUS versus DBS below.

Gamma/cyber knife thalamotomy

No evidence.

MRgFUS

One systematic review (Mohammed 2018[4]) reported pooled values from a meta-analysis comparing MRgFUS versus baseline (see Table 10). This suggested an improvement in function for patients treated with MRgFUS when compared to baseline. However, only one of the included studies was randomised and the remaining studies were observational (three retrospective/prospective studies) and therefore the pooled values were based mainly on lower level evidence.

One RCT (Elias 2016 reported in the Health Quality Ontario HTA 2018[1]) compared MRgFUS to a sham procedure (see Table 10). The study was rated as high quality and assessed functional disability in activities of daily living using the CRST tool (part C) at baseline, three months and 12 months. A reduction was seen in functional disability in the MRgFUS group compared with sham. This extended to 12 months post-treatment with improvements observed in all activities assessed within Part C with the exception of writing.[1]

MRgFUS versus DBS

The Health Quality Ontario HTA 2018[1] also summarised data from one retrospective observational study (Huss 2016; data taken from the Health Quality Ontario HTA report[1]) that compared MRgFUS with DBS (unilateral or bilateral). Although this was a lower evidence study an improvement in disability (CRST part C) was observed for both MRgFUS and DBS from baseline, no obvious differences were observed between the two different intervention groups (see Table 10).

A systematic review by Langford 2018[3] compared MRgFUS to unilateral DBS reporting data from six observational studies using a match-adjusted indirect comparison (see Table 10). Given the low level evidence included in the analysis and other issues with a cautious interpretation is advised, but overall no reliable evidence was found to support a difference between the two interventions with respect to functional disability (CRST part C).

Table 10: Summary of evidence on reduction in functional outcomes

Outcome	Author	No. of studies (type of study)	Average follow up time (years)	Intervention Mean score (SD)	Comparator Mean score (SD)	Mean difference, points (95% CI)	Intervention favoured (direction of the effect)	Quality of evidence (GRADE)
Systematic reviews with pooled effect sizes – 1st level evidence								
CRST part C	Mohammed 2018[4]	4 (RCT, PROS, RA) [14-17]	NR	**MRgFUS**	**Baseline (i.e. pre-treatment)**	69.1% (54.6 to 80.5%)[a]	MRgFUS	NR
RCTs – 2nd level evidence								
CRST part C	Health Quality Ontario HTA 2018[1] (Elias 2016[15])	1 (RCT)	Baseline	**MRgFUS** 16.5 (4.6)	**Sham** 16.0 (4.3)	NA	NA	NR
	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	3 months	**MRgFUS** 6.2 (5.6) MIB = 62%	**Sham** 15.6 (4.6) MIB = 3%	NR p<0.001	MRgFUS	HIGH
	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	1	**MRgFUS** 6.3 (6.2) MIB = 62%	NR	NA	NA	NR
Observational studies – 3rd level evidence								
CRST part C	Health Quality Ontario HTA 2018[1] (Huss 2016)[17]	1 (RA)	Baseline	**MRgFUS** 18.2 (NR)	**U-DBS** 18.9 (NR) **B-DBS** 19.9 (NR)	NA	NA	VERY LOW
CRST part C	Health Quality Ontario HTA 2018[1] (Huss 2016)[17]	1 (RA)	NR	**MRgFUS** 2.8 (NR) MIB = 85.4%[c]	**U-DBS** 3.2 (NR) MIB = 88.4%[c] **B-DBS** 2.3 (NR) MIB = 83.1%[c]	NR B-DBS vs U-DBS: p=0.42; B-DBS vs MRgFUS: p=0.59	B-DBS	VERY LOW

Outcome	Author	No. of studies (type of study)	Average follow up time (years)	Intervention Mean score (SD)	Comparator Mean score (SD)	Mean difference, points (95% CI)	Intervention favoured (direction of the effect)	Quality of evidence (GRADE)
CRST part C	Langford 2018[3] (Putzke 2005)[22]	1 (PROS)	1 month	**MRgFUS**	**U-DBS**	1.92 (-0.94 to 4.79)[b]	MRgFUS	NR
CRST part C	Langford 2018[3] (Putzke 2005)[22]	1 (PROS)	3 months	**MRgFUS**	**U-DBS**	-0.21 (-3.22 to 2.81) [b]	U-DBS	NR
CRST part C	Langford 2018[3] (Graff-Radford 2010)[23]	1 (PROS)	6 months	**MRgFUS**	**U-DBS**	-4.40 (-8.18 to -0.61) [b]	U-DBS	NR
CRST part C	Langford 2018[3] (Favilla 2012)[24]	1 (RA)	6 months	**MRgFUS**	**U-DBS**	-2.08 (-5.13 to 0.96) [b]	U-DBS	NR
CRST part C	Langford 2018[3] (Nazzaro 2012)[25]	1 (RA)	1	**MRgFUS**	**U-DBS**	-1.39 (-3.40 to 0.63) [b]	U-DBS	NR
CRST part C	Langford 2018[3] (Favilla 2012)[24]	1 (PROS)	1	**MRgFUS**	**U-DBS**	-1.55 (-5.79 to 2.70) [b]	U-DBS	NR
CRST part C	Langford 2018[3] (Blomstedt 2007)[20]	1 (PROS)	1	**MRgFUS**	**U-DBS**	0.39 (-2.53 to 3.30) [b]	MRgFUS	NR

[a] Pooled estimate of the percentage improvement;

[b] Matching-adjusted indirect comparison;

[c] Corresponds to statistically significant difference from baseline ($p<0.05$); B-DBS = bilateral deep brain stimulation; MIB = mean improvement vs. baseline; MRgFUS = Magnetic Resonance-Guided Focused Ultrasound thalamotomy; NA = not applicable; NR = not reported; PROS = prospective analysis RA = retrospective analysis; RCT = randomised controlled trial; U-DBS = unilateral deep brain stimulation

FAQ 3b: Will I be able to return to work?

No specific evidence related to time taken to return to work was identified.

FAQ 3c: Will I be able to drive/return to driving?

No specific evidence related to time taken to return to driving was identified.

FAQ 3d: Will my quality of life improve?

Quality of life was generally reported using the Quality of Life in Essential Tremor (QUEST) questionnaire (scores ranging from 0 to 100). This captures several aspects of quality of life including: communication, work and finances, hobbies and leisure, physical activities of daily living, and psychosocial wellbeing. The higher the QUEST score, the better a patient's quality of life.

A summary of the available evidence on quality life is reported in Table 11.

No invasive tremor treatment

No evidence found.

DBS

See comparison between MRgFUS and DBS below.

Gamma/cyber knife thalamotomy

No evidence found.

MRgFUS

The systematic review by Mohammed 2018[4, 5] reported pooled values.

The Heath Ontario HTA report[1] concluded that:

'People with essential tremor who had undergone MRgFUS neurosurgery reported positive experiences. They liked that it was a noninvasive procedure and reported a substantial reduction in tremor that resulted in an improvement in their quality of life.'

The report included evidence from one RCT (Elias 2017; data taken from Heath Ontario HTA report [1]) which compared differences in QUEST scores three months after MRgFUS in comparison with a sham procedure (see Table 11). The QUEST scores suggested that patients receiving MRgFUS experienced improved quality of life in comparison the sham treatment group (46% improvement from baseline for MRgFUS versus 3% improvement from baseline for sham; $p<0.001$). This improvement was also reported to be sustained at 12 months post-procedure for the MRgFUS group (49% improvement from baseline; note after three months patients in the sham group could crossover to receive MRgFUS so there are no data for sham at 12 months).

MRgFUS versus DBS

A retrospective study (Huss 2016 reported in the Health Quality Ontario HTA 2018[1]) that compared MRgFUS to bilateral DBS. This study was also reported in detail in the NICE IPG617 report[6] (see Table 11). Huss 2016 (data taken from Health Quality Ontario HTA 2018[1]) was a retrospective observational study and although between group comparisons were reported for QUEST scores (including sub-scores) the Health Quality Ontario HTA 2018[1] advises caution when interpreting these scores as there were '*significant between-groups differences at baseline in age and tremor severity …patients who underwent bilateral DBS were older and had more severe tremor*'. Similar improvements were reported for patients treated with MRgFUS and those treated with bilateral DBS.

The NICE IPG617 report[6] stated that there was no substantial difference in quality of life between MRgFUS (68% improvement in overall QUEST score from baseline) and bilateral DBS (72% improvement in overall QUEST score from baseline), though there was an improvement in the QUEST scores from baseline in both groups. This assessment was also based on the same retrospective study (Huss 2016 reported in NICE IPG617 report[6]). Table 11 summarises additional data for the QUEST sub-scores though again these should be interpreted with caution.

Other comparisons

No evidence was found comparing MRgFUS or DBS with gamma/cyber knife thalamotomy (stereotactic radiosurgery).

Table 11: Summary of evidence on quality of life

Outcome	Author	No. of studies (type of study)	Average follow up time (years)	Intervention Mean score (SD)	Comparator Mean score (SD)	Mean difference, points (95% CI)	Intervention favoured (direction of the effect)	Quality of evidence (GRADE)
Systematic reviews with pooled effect sizes – 1st level evidence								
QUEST score	Mohammed 2018[4]	4 (RCT, PROS, RA) [a12, 14, 15, 17]	NR	**MRgFUS**	**Baseline (i.e. pre-treatment)**	46.5% (36.4 to 56.9%); I^2=68.5%	MRgFUS	NR
RCTs – 2nd level evidence								
QUEST score	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	Baseline	**MRgFUS** 42.6 (18.3)	**Sham** 42.8 (19.5)	NA	NA	NR
	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	3 months	**MRgFUS** 23.1 (16.9) MIB = 46%	**Sham** 41.4 (19.4) MIB = 3%	-18.30 (-27.89 to -8.71)	MRgFUS	HIGH
	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	1	**MRgFUS** 21.7 (17.2) MIB = 49%	NR	NR	NA	NR
Observational studies – 3rd level evidence								
QUEST score	Health Quality Ontario HTA 2018[1] (Huss 2016)[17]	1 (RA)	MRgFUS (1) B-DBS (13 months) U-DBS (9 months)	**MRgFUS (n=15)** Improved by 68.0%[b]	**B-DBS (n=57)** Improved by 72.0%[b]	NR p>0.05	B-DBS	VERY LOW
Improvement in communication versus baseline	NICE IPG617[6] (Huss 2016)[17]	1 (RA)	MRgFUS (1) B-DBS (13 months) U-DBS (9 months)	**MRgFUS (n=15)** Improved by 37.6%	**B-DBS (n=57)** Improved by 46.9%[b]	NR p>0.05	B-DBS	NR
Improvement in work versus baseline	NICE IPG617[6] (Huss 2016)[17]	1 (RA)	MRgFUS (1) B-DBS (13 months) U-DBS (9 months)	**MRgFUS (n=15)** Improved by 51.7%[b]	**B-DBS (n=57)** Improved by 87.6%[b]	NR p>0.05	B-DBS	NR

Outcome	Author	No. of studies (type of study)	Average follow up time (years)	Intervention Mean score (SD)	Comparator Mean score (SD)	Mean difference, points (95% CI)	Intervention favoured (direction of the effect)	Quality of evidence (GRADE)
Improvement in hobbies versus baseline	NICE IPG617[6] (Huss 2016)[17]	1 (RA)	MRgFUS (1) B-DBS (13 months) U-DBS (9 months)	**MRgFUS (n=15)** Improved by 67.4%[b]	**B-DBS (n=57)** Improved by 67.5%[b]	NR p>0.05	NR	NR
Physical improvement versus baseline	NICE IPG617[6] (Huss 2016)[17]	1 (RA)	MRgFUS (1) B-DBS (13 months) U-DBS (9 months)	**MRgFUS (n=15)** Improved by 75.2%[b]	**B-DBS (n=57)** Improved by 76.7%[b]	NR p>0.05	B-DBS	NR
Social improvement versus baseline	NICE IPG617[6] (Huss 2016)[17]	1 (RA)	MRgFUS (1) B-DBS (13 months) U-DBS (9 months)	**MRgFUS (n=15)** Improved by 75.8%[b]	**B-DBS (n=57)** Improved by 72.9%[b]	NR p>0.05	MRgFUS	NR

[a] Pooled estimate of the percentage improvement

[b] Corresponds to statistically significant difference from baseline (p<0.05)

MIB = mean improvement vs. baseline; MRgFUS = Magnetic Resonance-Guided Focused Ultrasound thalamotomy; NA = not applicable; NR = not reported; PROS = prospective analysis; .= not significant; RA = retrospective analysis

FAQ 3: EVIDENCE SUMMARY

What will be the impact on my daily living?

FAQ 3a: Will I be able to return to my usual activities?

No evidence was found for GK.

One systematic review reported pooled values comparing functional disability of patient treated with MRgFUS compared to baseline. Although the pooled effects were based mainly on lower level evidence from observational studies (only one RCT was included) there appeared to be an improvement in function for patients treated with MRgFUS compared with baseline. High quality evidence from one RCT suggested that there was an improvement in functional disability for patients treated with MRgFUS compared with sham treatment. This improvement extended to one year after treatment and was observed in aspects of function assessed in part C of the CRST assessment, with the exception of writing.

Lower level evidence from one retrospective observational study and one match-adjusted indirect comparison suggested that there was no obvious difference between MRgFUS and DBS with respect to functional disability.

FAQ 3b: Will I be able to return to work?

No evidence was found.

FAQ 3c: Will I be able to drive/return to driving?

No evidence was found.

FAQ 3d: Will my quality of life improve?

No evidence was found for GK.

Evidence from one good quality RCT measured quality of life using the QUEST score and suggested that there was an obvious improvement of quality of life from baseline for MRgFUS and in comparison with patients in a sham treatment group. This improvement was sustained for up to one year after treatment.

Lower level evidence from one retrospective observational study suggested improvements in quality of life were similar between MRgFUS and bilateral DBS. Some differences within sub-scores for particular aspects of quality of life were reported, but the reliability of these is unclear.

FAQ 4: What are the possible adverse effects of treatment?

FAQ 4a: What side effects might I experience from my treatment?

A summary of the side effects experienced during each treatment is reported in Table 12 for procedural events (during and <1 month after the procedure) and Table 13 for short-term events (<3 months after the procedure).

No invasive tremor treatment

No evidence. Side effects will differ by individual drug treatment.

DBS

Patient information retrieved from the National Tremor Foundation website[8] reported that the risks associated with DBS include those associated with brain surgery in general (e.g. bleeding, stroke, death, anaesthetic related events), those associated with the DBS device (and having a foreign body implanted; e.g. stroke and intracranial haemorrhage, hemiplegia, headaches, infections and seizures), and finally those related to the electrical stimulations (can usually be reduced or eliminated; e.g. speech disturbances, dyskinesia and sensory disturbances).[8] Similar effects and risks were reported by patient information from the International Essential Tremor Foundation website.[9] Patient information from the website also advises that patients with DBS should avoid diathermy (e.g. as used during various surgeries, physical therapy for pain, and dentistry). The heat from diathermy can be transferred to the brain through the DBS electrode resulting in brain damage and rarely death.[9]

DBS is the only non-destructive invasive treatment, but does involve electrical leads being left inside the brain tissue. This can lead to risks and complications specific to DBS. The Health Quality Ontario HTA 2018[1] reported that across a sample of 57 patients there was one transient case of DBS lead erosion and two cases of transient haemorrhage.

Gamma/cyber knife thalamotomy

Little evidence was identified from the included studies on the potential adverse effects of GK treatment. A patient information leaflet from the International Essential Tremor Foundation website[9] suggests that most early side effects are usually temporary and may include tiredness and fatigue in the first few weeks. In addition, swelling in the locally affected area may result in headache, nausea, or vomiting.[9] The patient's scalp may also become irritated where the stereotactic frame was attached. Later effects may be experienced months after the procedure including neurological issues.

The Health Quality Ontario HTA 2018[1] reported that documented procedure-related adverse effects of GK thalamotomy include: mild numbness; hemiparesis; dysphagia, and death. The report states that there is a risk of progressive neurological deficits associated with radiation.

MRgFUS

Patient information from the International Essential Tremor Foundation website[9] suggests that the most common side effects of MRgFUS treatment (up to one third of patients in first year) are altered sensation and gait disturbances. Up to 5% of patients may also suffer from dysmetria (lack of coordination with undershooting and overshooting the intended position), ataxia and unsteadiness of gait for up to one year after treatment.[9]

The Health Quality Ontario HTA 2018[1] reported that MRgFUS across the four studies included in the review, the most frequent events experienced during the procedure were: vestibular symptoms (e.g.

dizziness, vertigo, nausea and vomiting). However, these symptoms resolved once the sonications were completed. One of the studies (Elias 2016; data taken from Health Quality Ontario HTA 2018;[1] n=15) also reported minor adverse events associated with the use of a stereotactic head frame in order to keep the patients head still and enable the precise location of the target area for treatment (see Table 12). These events included: headaches of more than 24 hours duration (27%; n=4); scalp numbness (27%; n=4); pin site laceration (7%; n=2); swelling around the eyes (7%; n=1); and scalp burns from pin site MRI heating (13%; n=2). However, all of these events resolved without the need for further intervention. Other reported events reported in the studies of MRgFUS included: paraesthesia or numbness of the face or fingers. Problems with gait or motor disturbances were more rarely encountered. Overall, most events reported shortly after the procedure were recorded as transient and often related to postoperative swelling near the lesion site which resolved by the next follow-up. In conclusion, the authors reported that MRgFUS had a favourable safety profile:

'*MRgFUS neurosurgery is an effective and generally safe treatment option for moderate to severe, medication-refractory essential tremor.*'

A further review by Mohammed 2018[4] (erratum in Mohammed 2018[5]) reported similar findings with dizziness (43.4%) being the most common in-procedure complication, followed by nausea and vomiting in (26.8% - pooled estimate). Other common in-procedure complications included: headache, sensation of warmth in the scalp, flushing and paraesthesia. However, these in-procedure complications quickly resolved after the procedure was completed. Post-procedure up to three months suggested that ataxia (32.8% - pooled estimate) was the common complication, followed by paraesthesia (25.1% - pooled estimate). However, for many patients the ataxia had significantly recovered at later time points. Other complications, included: dysarthria (4.1% - pooled estimate), limb weakness (5.6% - pooled estimate), dysmetria (8.4% - pooled estimate), tinnitus (5.35% - pooled estimate), fatigue (5.35% - pooled estimate), and dysgeusia (4.4% - pooled estimate). The authors concluded that overall MRgFUS had 'an acceptable complication rate'.

Table 12: Summary of evidence on adverse effects – procedural effects

Event type	Author	No of studies (type of study)	Average follow up time (years)	Intervention (n) n (%) with event	Comparator (n) n (%) with event	p-value	Quality of evidence (GRADE)
No invasive tremor treatment							
No evidence							
DBS							
No evidence							
Gamma/cyber knife thalamotomy							
No evidence							
MRgFUS							
Anxiety	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	Procedural Event	**MRgFUS (n=56)** 3 (5)	**Sham (n=20)** 2 (10)	NR	NR
Anxiety	Bond 2017	1 (RCT)	Procedural Event	**MRgFUS (n=20) 1 (10)**	**Sham (n=7) 0**	NR	NR
Back pain	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	Procedural Event	**MRgFUS (n=56)** 5 (9)	**Sham (n=20)** 1 (5)	NR	NR
Head or neck or shoulder pain	Bond 2017	1 (RCT)	Procedural Event	**MRgFUS (n=20) 4 (20)**	**Sham (n=7) 1 (14)**	NR	NR
Dizziness	Mohammed 2018[5]	8 (1 RCT, 5 RA, 2 PROS) [12-19]	Procedural Event	**MRgFUS (NR)** NR (43.4); I^2=77.5%	**Baseline (i.e. pre-treatment)**	NR	NR
Headache	Mohammed 2018[5]	8 (1 RCT, 5 RA, 2 PROS) [12-19]	Procedural Event	**MRgFUS (NR)** 20 (NR)	**Baseline (i.e. pre-treatment)**	NR	NR
Headache	Bond 2017	1 (RCT)	Procedural Event	**MRgFUS (n=20) 12 (60)**	**Sham (n=7) 3 (43)**	NR	NR

Event type	Author	No of studies (type of study)	Average follow up time (years)	Intervention (n) n (%) with event	Comparator (n) n (%) with event	p-value	Quality of evidence (GRADE)
Head pain or heat sensation	Bond 2017	1 (RCT)	Procedural Event	**MRgFUS (n=20) 3 (15)**	**Sham (n=7) 0 (14)**	NR	NR
Head discomfort	Health Quality Ontario HTA 2018[1] (Elias 2016) [15]	1 (RCT)	Procedural Event	**MRgFUS (n=56)** 17 (30)	**Sham (n=20)** 0 (0)	NR	NR
Lightheadedness	Bond 2017	1 (RCT)	Procedural Event	**MRgFUS (n=20) 2 (10)**	**Sham (n=7) 0**	NR	NR
Nausea	Health Quality Ontario HTA 2018[1] (Elias 2016) [15]	1 (RCT)	Procedural Event	**MRgFUS (n=56)** 11 (20)	**Sham (n=20)** 2 (10)	NR	NR
Nausea and vomiting	Mohammed 2018[5]	8 (1 RCT, 5 RA, 2 PROS) [12-19]	Procedural Event	**MRgFUS (NR)** NR (26.8); I^2=55.5%	**Baseline (i.e. pre-treatment)**	NR	NR
Stomach pain or nausea or emesis	Bond 2017	1 (RCT)	Procedural Event	**MRgFUS (n=20) 4 (20)**	**Sham (n=7) 1 (14)**	NR	NR
Periorbital swelling	Bond 2017	1 (RCT)	Procedural Event	**MRgFUS (n=20) 2 (10)**	**Sham (n=7) 0**	NR	NR
Scalp tingling	Health Quality Ontario HTA 2018[1] (Elias 2016) [15]	1 (RCT)	Procedural Event	**MRgFUS (n=56)** 4 (7)	**Sham (n=20)** 1 (5)	NR	NR
Stereotactic frame problems (in-site oedema, pain, or bursting etc.)	Health Quality Ontario HTA 2018[1] (Elias 2016) [15]	1 (RCT)	Procedural Event	**MRgFUS (n=56)** 17 (30)	**Sham (n=20)** 7 (35)	NR	NR
Vertigo	Health Quality Ontario HTA	1 (RCT)	Procedural Event	**MRgFUS (n=56)** 12 (21)	**Sham (n=20)** 0 (0)	NR	NR

Event type	Author	No of studies (type of study)	Average follow up time (years)	Intervention (n) n (%) with event	Comparator (n) n (%) with event	p-value	Quality of evidence (GRADE)
	2018[1] (Elias 2016) [15]						
Dizziness or vertigo	Bond 2017	1 (RCT)	Procedural Event	**MRgFUS (n=20)** **8 (40)**	**Sham (n=7)** **1 (14)**	NR	NR

B-DBS = bilateral deep brain stimulation; DBS = deep brain stimulation; MRgFUS = Magnetic Resonance-Guided Focused Ultrasound thalamotomy; NA = not applicable; NR = not reported; RA = retrospective analysis; RCT= randomised controlled trial; U-DBS = unilateral deep brain stimulation

Table 13: Summary of evidence on adverse effects – short term events (within first 12 months post procedure and at 12 months)

Event type	Author	No of studies (type of study)	Average follow up time (years)	Intervention - n (%) with event	Comparator - n (%) with event	p-value	Quality of evidence (GRADE)
No invasive tremor treatment							
No evidence							
DBS							
See MRgFUS versus DBS							
Gamma/cyber knife thalamotomy							
No evidence							
MRgFUS (within first 12 months)							
Ataxia	Mohammed 2018[5]	9 (1 RCT, 6 RA, 2 PROS)[11-19]	3 months	**MRgFUS (NR)** NR (32.8); I^2=52.1%	**Baseline (i.e. pre-treatment)**	NR	NR
Ataxia, noted objectively on examination	Health Quality Ontario HTA 2018[1] (Elias 2016) [15]	1 (RCT)	Within first 12 months	**MRgFUS (n=56)** 11 (20)	**Sham (n=20)** 0 (0)	NR	NR
Contralateral weakness	Health Quality Ontario HTA 2018[1] (Elias 2016) [15]	1 (RCT)	Within first 12 months	**MRgFUS (n=56)** 2 (4)	**Sham (n=20)** 0 (0)	NR	NR

Event type	Author	No of studies (type of study)	Average follow up time (years)	Intervention - n (%) with event	Comparator - n (%) with event	p-value	Quality of evidence (GRADE)
Dysmetria of the limb (lack of coordination of movements, i.e. over- and undershooting of intended position)	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	Within first 12 months	**MRgFUS (n=56)** 7 (12)	**Sham (n=20)** 0 (0)	NR	NR
Dysarthria (difficulty speaking)	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	Within first 12 months	**MRgFUS (n=56)** 1 (2)	**Sham (n=20)** 0 (0)	NR	NR
Dysphagia (swallowing problems)	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	Within first 12 months	**MRgFUS (n=56)** 1 (2)	**Sham (n=20)** 0 (0)	NR	NR
Disequilibrium sensation	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	Within first 12 months	**MRgFUS (n=56)** 5 (9)	**Sham (n=20)** 0 (0)	NR	NR
Fatigue	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	Within first 12 months	**MRgFUS (n=56)** 3 (5)	**Sham (n=20)** 1 (5)	NR	NR
Gait disturbance (any, objective or subjective)	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	Within first 12 months	**MRgFUS (n=56)** 20 (36)	**Sham (n=20)** 1 (5)	NR	NR
Headache (lasting >1 day)	Health Quality Ontario HTA	1 (RCT)	Within first 12 months	**MRgFUS (n=56)** 8 (14)	**Sham (n=20)** 4 (20)	NR	NR

Event type	Author	No of studies (type of study)	Average follow up time (years)	Intervention - n (%) with event	Comparator - n (%) with event	p-value	Quality of evidence (GRADE)
	2018[1] (Elias 2016)[15]						
Paraesthesia (abnormal sensation in the skin (e.g. pins and needles))	Mohammed 2018[5]	9 (1 RCT, 6 RA, 2 PROS)[11-19]	3 months	**MRgFUS (NR)** NR (25.1); I^2=79.4%	**Baseline (i.e. pre-treatment)**	NR	NR
Paraesthesia or numbness, any region (e.g. face, hand, fingers, leg)	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	Within first 12 months	**MRgFUS (n=56)** 21 (38)	**Sham (n=20)** 0 (0)	NR	NR
Paraesthesia/numbness – Face and hand	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	Within first 12 months	**MRgFUS (n=56)** 6 (11)	**Sham (n=20)** 0 (0)	NR	NR
Paraesthesia/numbness – Face, lips and tongue	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	Within first 12 months	**MRgFUS (n=56)** 8 (14)	**Sham (n=20)** 0 (0)	NR	NR
Paraesthesia/numbness – Hand and fingers	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	Within first 12 months	**MRgFUS (n=56)** 6 (11)	**Sham (n=20)** 1 (5)	NR	NR
Paraesthesia/numbness - Leg	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	Within first 12 months	**MRgFUS (n=56)** 1 (2)	**Sham (n=20)** 0 (0)	NR	NR
Subjective unsteadiness	Health Quality Ontario HTA 2018[1] (Elias 2016)	1 (RCT)	Within first 12 months	**MRgFUS (n=56)** 9 (16)	**Sham (n=20)** 1 (5)	NR	NR

Event type	Author	No of studies (type of study)	Average follow up time (years)	Intervention - n (%) with event	Comparator - n (%) with event	p-value	Quality of evidence (GRADE)
	[15]						
Taste disturbance/loss of taste	Health Quality Ontario HTA 2018[1] (Elias 2016) [15]	1 (RCT)	Within first 12 months	**MRgFUS (n=56)** 3 (5)	**Sham (n=20)** 0 (0)	NR	NR
Tinnitus	Health Quality Ontario HTA 2018[1] (Elias 2016) [15]	1 (RCT)	Within first 12 months months	**MRgFUS (n=56)** 3 (5)	**Sham (n=20)** 0 (0)	NR	NR
MRgFUS (at 12 months)							
Ataxia, noted objectively on examination	Health Quality Ontario HTA 2018[1] (Elias 2016) [15]	1 (RCT)	at 12 months	**MRgFUS (n=56)** 2 (4)	**Sham (n=20)** 0 (0)	NR	NR
Contralateral weakness	Health Quality Ontario HTA 2018[1] (Elias 2016) [15]	1 (RCT)	at 12 months	**MRgFUS (n=56)** 1 (2)	**Sham (n=20)** 0 (0)	NR	NR
Dysmetria of the limb (lack of coordination of movements, i.e. over- and undershooting of intended position)	Health Quality Ontario HTA 2018[1] (Elias 2016) [15]	1 (RCT)	at 12 months	**MRgFUS (n=56)** 2 (4)	**Sham (n=20)** 0 (0)	NR	NR
Dysarthria (difficulty speaking)	Health Quality Ontario HTA 2018[1] (Elias 2016) [15]	1 (RCT)	at 12 months	**MRgFUS (n=56)** 0 (0)	**Sham (n=20)** 0 (0)	NR	NR

Event type	Author	No of studies (type of study)	Average follow up time (years)	Intervention - n (%) with event	Comparator - n (%) with event	p-value	Quality of evidence (GRADE)
Dysphagia (swallowing problems)	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	at 12 months	**MRgFUS (n=56)** 0 (0)	**Sham (n=20)** 0 (0)	NR	NR
Disequilibrium sensation	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	at 12 months	**MRgFUS (n=56)** 1 (2)	**Sham (n=20)** 0 (0)	NR	NR
Fatigue	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	at 12 months	**MRgFUS (n=56)** 0 (0)	**Sham (n=20)** 1 (5)	NR	NR
Gait disturbance (any, objective or subjective)	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	at 12 months	**MRgFUS (n=56)** 5 (9)	**Sham (n=20)** 1 (5)	NR	NR
Headache (lasting >1 day)	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	at 12 months	**MRgFUS (n=56)** 0 (0)	**Sham (n=20)** 4 (20)	NR	NR
Paraesthesia or numbness, any region (e.g. face, hand, fingers, leg)	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	at 12 months	**MRgFUS (n=56)** 8 (14)	**Sham (n=20)** 0 (0)	NR	NR
Paraesthesia/numbness – Face and hand	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	at 12 months	**MRgFUS (n=56)** 5 (9)	**Sham (n=20)** 0 (0)	NR	NR
Paraesthesia/numbness – Face, lips	Health Quality Ontario HTA	1 (RCT)	at 12 months	**MRgFUS (n=56)** 2 (4)	**Sham (n=20)** 0 (0)	NR	NR

Event type	Author	No of studies (type of study)	Average follow up time (years)	Intervention - n (%) with event	Comparator - n (%) with event	p-value	Quality of evidence (GRADE)
and tongue	2018[1] (Elias 2016)[15]						
Paraesthesia/numbness – Hand and fingers	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	at 12 months	**MRgFUS (n=56)** 1 (2)	**Sham (n=20)** 1 (5)	NR	NR
Paraesthesia/numbness - Leg	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	at 12 months	**MRgFUS (n=56)** 0 (0)	**Sham (n=20)** 0 (0)	NR	NR
Subjective unsteadiness	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	at 12 months	**MRgFUS (n=56)** 3 (5)	**Sham (n=20)** 1 (5)	NR	NR
Taste disturbance/loss of taste	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	at 12 months	**MRgFUS (n=56)** 2 (4)	**Sham (n=20)** 0 (0)	NR	NR
Tinnitus	Health Quality Ontario HTA 2018[1] (Elias 2016)[15]	1 (RCT)	at 12 months	**MRgFUS (n=56)** 0 (0)	**Sham (n=20)** 0 (0)	NR	NR
MRgFUS versus DBS							
Balance problems	Health Quality Ontario HTA 2018[1] (Kim 2017)[11]	1 (RA)	1 month	**MRgFUS (n=23)** 1 (4.3)	**DBS (n=19)** NR	NR	VERY LOW
DBS lead erosion	Health Quality Ontario HTA 2018[1] (Huss 2016)	1 (RA)	1	**MRgFUS (n=15)** NA	**B-DBS (n=57)** 1 (2) **U-DBS (n=13)**	NR	NR

Event type	Author	No of studies (type of study)	Average follow up time (years)	Intervention - n (%) with event	Comparator - n (%) with event	p-value	Quality of evidence (GRADE)
	[17]				0 (0)		
Dysarthria	Health Quality Ontario HTA 2018[1] (Huss 2016) [17]	1 (RA)	3 months	**MRgFUS (n=15)** 1 (7)	**B-DBS (n=57)** 10 (18) **U-DBS (n=13)** 1 (8)	NR	NR
Gait instability	Health Quality Ontario HTA 2018[1] (Huss 2016) [17]	1 (RA)	3 months	**MRgFUS (n=15)** 5 (33)	**B-DBS (n=57)** 10 (18) **U-DBS (n=13)** 11 (85)	NR	NR
Headache	Health Quality Ontario HTA 2018[1] (Huss 2016) [17]	1 (RA)	3 months	**MRgFUS (n=15)** 9 (60)	**B-DBS (n=57)** 0 (0) **U-DBS (n=13)** 0 (0)	NR	NR
Haemorrhage	Health Quality Ontario HTA 2018[1] (Huss 2016) [17]	1 (RA)	3 months	**MRgFUS (n=15)** 0 (0)	**B-DBS (n=57)** 2 (4) **U-DBS (n=13)** 0 (0)	NR	NR
Loss of taste	Health Quality Ontario HTA 2018[1] (Kim 2017) [11]	1 (RA)	1 month	**MRgFUS (n=23)** 1 (4.3)	**DBS (n=19)** NR	NR	VERY LOW
Mental status change	Health Quality Ontario HTA 2018[1] (Huss 2016) [17]	1 (RA)	3 months	**MRgFUS (n=15)** 0 (0)	**B-DBS (n=57)** 3 (5) **U-DBS (n=13)** 1 (8)	NR	NR
Mild facial paresis	Health Quality Ontario HTA 2018[1] (Kim 2017)[11]	1 (RA)	1 month	**MRgFUS (n=23)** 1 (4.3)	**DBS (n=19)** 1 (5.3)	NR	VERY LOW
Nausea or	Health Quality	1 (RA)	3 months	**MRgFUS (n=15)**	**B-DBS (n=57)**	NR	NR

Event type	Author	No of studies (type of study)	Average follow up time (years)	Intervention - n (%) with event	Comparator - n (%) with event	p-value	Quality of evidence (GRADE)
vomiting	Ontario HTA 2018[1] (Huss 2016)[17]			8 (53)	0 (0) **U-DBS (n=13)** 0 (0)		
Stereotactic frame problems (in-site oedema, pain, or bursting etc.)	Health Quality Ontario HTA 2018[1] (Huss 2016)[17]	1 (RA)	3 months	**MRgFUS (n=15)** 2 (13)	**B-DBS (n=57)** 0 (0) **U-DBS (n=13)** 0 (0)	NR	NR
Vertigo	Health Quality Ontario HTA 2018[1] (Huss 2016)[17]	1 (RA)	3 months	**MRgFUS (n=15)** 11 (73)	**B-DBS (n=57)** 0 (0) **U-DBS (n=13)** 0 (0)	NR	NR
Warm or flushed feeling	Health Quality Ontario HTA 2018[1] (Huss 2016)[17]	1 (RA)	3 months	**MRgFUS (n=15)** 4 (27)	**B-DBS (n=57)** 0 (0) **U-DBS (n=13)** 0 (0)	NR	NR
Weakness	Health Quality Ontario HTA 2018[1] (Huss 2016)[17]	1 (RA)	3 months	**MRgFUS (n=15)** 1 (7)	**B-DBS (n=57)** 4 (7) **U-DBS (n=13)** 1 (8)	NR	NR

B-DBS = bilateral deep brain stimulation; DBS = deep brain stimulation; MRgFUS = Magnetic Resonance-Guided Focused Ultrasound thalamotomy; NR = not reported; RA = retrospective analysis; RCT= randomised controlled trial; U-DBS = unilateral deep brain stimulation

FAQ 4b: What long-term risks are associated with treatment?

Longer-term/persistent adverse events or complications associated with the treatments are summarised in Table 14.

No invasive tremor treatment

No evidence identified. Side effects will differ by individual drug treatment.

DBS

DBS in the only invasive treatment where electrical leads are left inside the brain tissue. This can lead to risks and complications specific to DBS. The Health Quality Ontario HTA 2018[1] identified three such complications in two retrospective studies with a total of 89 patients: DBS hardware infection (n=1 at 12 months) and DBS lead erosion (n=2 at 12 months). The most common adverse effects associated with DBS were gait instability/balance problems (15.8%). Other events (dysarthria; forearm muscle twitch; mental health status change; paraesthesia) experienced at 12 months are reported in Table 14, but the incidences of these events were generally low (usually less than 10% of the sample population). All side effects apart the balance problems (Kim 2017) were reported for the B-DBS arm and not for the U-DBS arm in Huss 2016.

Gamma/cyber knife thalamotomy

The Health Quality Ontario HTA 2018[1] reported that the effects of GK thalamotomy do not appear until weeks or months after the procedure. A systematic review by Schreglmann 2018[2] reported that the rate of persistent side effects after unilateral GK surgery (n=153) was 1.8% (± 3.0%). The most common persistent effects included: speech and swallowing difficulties (1.3% - pooled estimate) and sensory changes (0.7% - pooled estimate) (see Table 14). The Health Quality Ontario HTA 2018[1] reported that there is a risk of progressive neurological deficits associated with the use of radiation during the GK procedure.

MRgFUS

The HTA report by Health Quality Ontario HTA 2018[1] concluded that 'MRgFUS neurosurgery has a favourable safety profile' with very few serious complications.

A systematic review by Mohammed 2018[4] (erratum in Mohammed 2018[5]) at 12 months posttreatment the most common persisting complication was paraesthesia (15.3% - pooled estimate), following by ataxia (10.5% - pooled estimate).

In a second systematic review by Schreglmann 2018,[2] 13 cohorts (n=273) were identified for the safety analysis. The overall rate of reported persistent side effects after MRgFUS vim was 18.7% (± 16.2%). These most commonly included persistent sensory changes (14.6% - pooled estimate) (see Table 14).

MRgFUS versus DBS

The Health Quality Ontario HTA 2018[1] reported that at 12 months the lowest complication rate occurred in the MRgFUS group in comparison with the DBS group (respectively 4.4% and 21.1%; $p<0.01$). However, when non-modifiable complications associated with DBS were included there was no longer a significant difference between the two procedures in terms of overall side effects. Further details of the study comparing MRgFUS and DBS (unilateral and bilateral) are reported in Table 14.

Table 14: Summary of evidence on adverse effects after treatment – long-term (>12months) and/or persistent effects/complications

Outcome	Author	No of studies (type of study)	Average follow up time (years)	Intervention - n (%) with event	Comparator - n (%) with event	p-value[a]	Quality of evidence (GRADE)
No invasive tremor treatment							
No evidence							
DBS							
See MRgFUS versus DBS							
Gamma/cyber knife thalamotomy							
Persistent sensory changes only	Schreglmann 2018[2]	6 (NR)	Mean 1.5	**GK (vim) (n=153)** 1 (0.7)	**Baseline (i.e. pre-treatment)**	NR	NR
Persistent speech and swallowing difficulties	Schreglmann 2018[2]	6 (NR)	Mean 1.5	**GK (vim) (n=153)** 2 (1.3)	**Baseline (i.e. pre-treatment)**	NR	NR
MRgFUS							
Ataxia - persisting	Mohammed 2018[5]	9 (1 RCT, 6 RA, 2 PROS)	1	**MRgFUS (NR)** NR (10.5); I^2=0%)	**Baseline (i.e. pre-treatment)**	NR	NR
Paraesthesia - persisting	Mohammed 2018[5]	9 (1 RCT, 6 RA, 2 PROS)	1	**MRgFUS (NR)** NR (15.3); I^2=0%	**Baseline (i.e. pre-treatment)**	NR	NR
Persistent speech and swallowing difficulties	Schreglmann 2018[2]	3 (NR)	Mean 10 months	**MRgFUS (vim) (n=82)** 0 (0)	**Baseline (i.e. pre-treatment)**	NR	NR
Persistent sensory changes only	Schreglmann 2018[2]	3 (NR)	Mean 10 months	**MRgFUS (vim) (n=82)** 12 (14.6)	**Baseline (i.e. pre-treatment)**	NR	NR

Outcome	Author	No of studies (type of study)	Average follow up time (years)	Intervention - n (%) with event	Comparator - n (%) with event	p-value[a]	Quality of evidence (GRADE)
MRgFUS versus DBS							
Balance problems	Health Quality Ontario HTA 2018[1] (Kim 2017)[11]	1 (RA)	1	**MRgFUS (n=23)** NR	**DBS (n=19)** 3 (15.8)	NR	VERY LOW
DBS lead erosion	Health Quality Ontario HTA 2018[1] (Huss 2016)[17]	1 (RA)	1	**MRgFUS (n=15)** NA	**B-DBS (n=57)** 2 (13) **U-DBS (n=13)** 0 (0)	NR	NR
Dysarthria	Health Quality Ontario HTA 2018[1] (Huss 2016)[17]	1 (RA)	1	**MRgFUS (n=15)** 0 (0)	**B-DBS (n=57)** 6 (11) **U-DBS (n=13)** 0 (0)	NR	NR
Forearm muscle twitch	Health Quality Ontario HTA 2018[1] (Kim 2017)[11]	1 (RA)	1	**MRgFUS (n=15)** Not applicable	**DBS (n=19)** 1 (5.3)	NR	VERY LOW
Mental health status change	Health Quality Ontario HTA 2018[1] (Huss 2016)[17]	1 (RA)	1	**MRgFUS (n=15)** 0 (0)	**B-DBS (n=57)** 3 (5) **U-DBS (n=13)** 0 (0)	NR	NR
Paraesthesia (any)	Health Quality Ontario HTA 2018[1] (Huss 2016)[17]	1 (RA)	1	**MRgFUS (n=15)** 3 (20)	**B-DBS (n=57)** 1 (2) **U-DBS (n=13)** 2 (15)	NR	NR
Very mild facial paresis	Health Quality Ontario HTA 2018[1] (Kim 2017)[11]	1 (RA)	1	**MRgFUS (n=23)** 1 (4.3)	**DBS (n=19)** NR	NR	VERY LOW

Outcome	Author	No of studies (type of study)	Average follow up time (years)	Intervention - n (%) with event	Comparator - n (%) with event	p-value[a]	Quality of evidence (GRADE)
Weakness	Health Quality Ontario HTA 2018[1] (Huss 2016)[17]	1 (RA)	1	**MRgFUS (n=15)** 0 (0)	**B-DBS (n=57)** 1 (2) **U-DBS (n=13)** 0 (0)	NR	NR

B-DBS = bilateral deep brain stimulation; DBS = deep brain stimulation; MRgFUS = Magnetic Resonance-Guided Focused Ultrasound thalamotomy; NR = not reported; RA = retrospective analysis; RCT= randomised controlled trial; U-DBS = unilateral deep brain stimulation

FAQ 4: EVIDENCE SUMMARY

***What are the possible adverse effects of treatment*?**

FAQ 4a: What side effects might I experience from my treatment?

The Health Quality Ontario HTA reported that DBS is the only non-destructive treatment but does involve electrical leads being inserted into the brain. This may in some circumstances leave to transient cases of lead erosion and haemorrhage though the number of cases was low in one small study (n=57 patients; one case of lead erosion and two cases of haemorrhage).

Little evidence was identified on the adverse effects of GK treatment. The Health Quality Ontario HTA reported that documents procedure-related adverse effects include: mild numbness, hemiparesis, dysphagia and death. The report also suggests that later effects included progressive neurological effects may results from the use of radiation.

The Health Quality Ontario HTA reported that across four studies the most frequent events experienced with MRgFUS were vestibular symptoms (dizziness, vertigo, nausea and vomiting) related to the ultrasound sonications. These disappeared once the procedure was completed. Other adverse effects included paraesthesia or numbness of the face or fingers. Similar findings were reported in a systematic review, which reported the most common place effects up to three months after MRgFUS were ataxia and paraesthesia which resolved at later time points.

Adverse events related to the use of a stereotactic frame were also reported for both DBS and MRgFUS, but these were considered mild and transient after treatment was completed.

FAQ 4b: What long-term risks are associated with treatment?

Evidence from two retrospective studies suggested a small number of hardware related adverse events in patients treated with DBS, including infection and lead erosion. The most common adverse effects at one year after treatment were gait instability/balance problems with low levels of dysarthria, forearm muscle twitch, mental health status change, and paraesthesia.

The Health Quality Ontario HTA report suggested that adverse effects of GK thalamotomy do not appear until weeks or months after the procedure and can be radiation related. One systematic review reported the most common persistent side effects after unilateral GK were speech and swallowing difficulties and sensory changes.

A systematic review reported that at 12 months the most common persisting side effects after MRgFUS were sensory changes and that a similar level of persistent complications was observed overall for MRgFUS and DBS.

3.3 ASSESSMENT OF THE CLINICAL REVIEW EVIDENCE

A summary of studies providing clinical evidence is set out in Table 15 below. Studies which merely provided descriptive evidence are not listed here. Only information on the evidence relevant for this report is presented.

Table 15: Overview of the clinical evidence

Study ID	Participants Inclusion criteria	Intervention	Comparators	Outcomes	Study Design	Follow- up (years)
Health Quality Ontario 2018[1]	• English-language full-text publications • Studies published prior to April 11, 2017 • Randomised controlled trials, systematic reviews, and non-randomised studies of MRgFUS neurosurgery alone or MRgFUS neurosurgery compared with one or more of the following: • Radiofrequency thalamotomy • DBS (unilateral or bilateral) • GK thalamotomy • Control intervention (e.g., sham)	MRgFUS	Sham, U-DBS, B-DBS	Upper extremity tremor; overall tremor severity; improvement in total CRST score; tremor abolition; complete tremor abolition; tremor recurrence; improvement in functional disability; quality of life score (QUEST); adverse events	SR	1 month up to 1 year
NICE IPG617 2018[6]	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. Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy. Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.	MRgFUS	U-DBS, B-DBS	CRST part A; CRST part B; improvement in the treated hand; improvement in total tremor; CRST total; improvement in communication, work, hobbies, physical and social	SR	MRgFUS: up to 1 B-DBS: up to 13 months U-DBS: up to 9 months Sham: up to 3 months
NICE IPG606 2018 [7]	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical	MRgFUS	Sham	Tremor subscore (CRST A+B), treated hand; CRST total	SR	3 months

Study ID	Participants Inclusion criteria	Intervention	Comparators	Outcomes	Study Design	Follow- up (years)
	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. Patients with moderate to severe tremor in Parkinson's disease. Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy. Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.					
Mohammed 2018[4] and erratum[5]	The inclusion criteria consist of the presence of bilateral postural tremor with or without kinetic component tremor, involving hands and forearms, that is visible and persistent-lasting for more than 5 years. The diagnosed cases of ET that were treated with MRgFUS were included in the study. All the cases that were treated with MRgFUS were refractory to medical therapy. Medication-refractory tremor was defined as persistent disabling tremor despite at least 2 trials of a full-dose therapeutic medication, 1 of which had to include propranolol or primidone. For the purpose of statistical analysis, only studies that assessed the tremor outcome by using the CRST were included. The diagnosis of ET was	MRgFUS	baseline	CRST total; CRST part C; Improvement in QUEST score; AEs	MA	Adverse events up to 1 year, for other outcomes not reported

Study ID	Participants Inclusion criteria	Intervention	Comparators	Outcomes	Study Design	Follow- up (years)
	based on the Movement Disorder Society's consensus statement.					
Schreglmann 2018[2]	Cohorts reporting a minimum of five patients of or above the age of 18 with a tremor diagnosis of confirmed aetiology, subjected to unilateral or bilateral lesional functional neurosurgery in a central neuroanatomical structure (thalamus, pallidum, subthalamic nucleus, alternative subcortical targets) by means of an intracerebral lesion, either by incisional (placement of a stylette, leukotome, cryosurgery or radiofrequency (RF) probe after skull opening) or incisionless (MRgFUS, GK) means. Data from peer-reviewed randomised controlled trials (RCTs), meta-analyses, case-control, prospective and retrospective case series were included in the analysis, while letters, abstracts and editorials were not.	MRgFUS, GK	Baseline	Change in upper limb tremor severity, AEs	MA and SR	Adverse events up to 1.5 years, for other outcomes not reported
Langford 2018[3]	• Adult patients with medication-refractory essential tremor • Magnetic resonance-guided focussed ultrasound (Exablate®), Unilateral DBS of the vim, Radiofrequency thalamotomy, Stereotactic radiosurgery techniques including Gamma Knife® and CyberKnife® • Clinical trials, systematic reviews or NMAs including potentially relevant studies were included in the review for the purpose of identifying any additional studies not identified in the database searches, but were excluded following further examination and not	MRgFUS	U-DBS	Total CRST score; CRST part C	SR and indirect comparison	Up to 1 year

Study ID	Participants Inclusion criteria	Intervention	Comparators	Outcomes	Study Design	Follow- up (years)
	extracted. HTAs presenting primary HRQoL (e.g. utilities) and cost data were extracted. If no primary data were presented in the HTA but it included a relevant systematic literature review, the reference list was hand-searched • Publications in the English language only • Journal articles published after 01/01/1990 • Conference abstracts published before 2014					

AE = adverse event; B-DBS = bilateral deep brain stimulation; CRST = clinical rating scale for tremor; ET = essential tremor; GK = gamma knife; HRQoL = health-related quality of life; HTA = health technology assessment; MA = meta-analysis; MRgFUS = Magnetic Resonance-Guided Focused Ultrasound thalamotomy; QUEST = Quality of Life in Essential Tremor; RCT = randomised controlled trial; SR = systematic review; U-DBS = unilateral deep brain stimulation

4. DISCUSSION

4.1 SUMMARY OF MAIN FINDINGS

A summary of the main findings of the review and the level of evidence to support the findings is reported in Table 16. For tremor-dominant PD only evidence on the effect of MRgFUS compared to GK, DBS, or vs. no invasive tremor treatment on the effect on tremor were extracted based on evidence based on RCTs.

Table 16: Summary of evidence (Data are on essential tremor unless specified otherwise)

Evidence	MRgFUS	DBS		GK	Notes
FAQ 2: Will my symptoms get better?					
Will my tremor improve?/ Will the function of my limbs improve?					
Essential tremor					
Tremor abolition	✓	✓(mixed U-DBS and B-DBS)		NI	Based on one retrospective analysis. Sustained treatment effect was reported in all groups at both 1 month and 12 months postoperatively.
Tremor recurrence	-	-		NI	Based on very low quality of evidence. Twelve months after surgery, one patient who had undergone MRgFUS and one who had undergone DBS experienced tremor recurrence.
Overall tremor severity	✓	✓(mixed U-DBS and B-DBS)		NI	In one study, patients who had undergone MRgFUS, had lower overall CRST scores at baseline in comparison to DBS patients. This result is based on all three levels of evidence.
Upper limb tremor severity (movement)	+	NI		+	Result for MRgFUS is based on one RCT and one indirect comparison, while result for GK is based on one indirect comparison of six cohorts which has high level of heterogeneity (I^2=92%).
Hand tremor severity	✓	✓ U-DBS	✓ B-DBS	NI	Based on one retrospective analysis where results were assessed via CRST part A. In the same study, another treated hand assessment showed that all treatments improved symptoms from baseline, but no differences between treatments were explored.
Action/tasks tremor	✓ (better than B-DBS)	✓ (better than B-DBS)	✓ B-DBS	NI	Based on one retrospective analysis where results were assessed via CRST part B.
Parkinson's disease					
Overall tremor severity	+	NI		NI	In a randomised controlled trial, comparing MRgFUS to sham the tremor subscore statistically improved by a median 62%. Also, resting and postural or action tremors were improved significantly when compared to baseline.
FAQ 3: What will be the impact on my daily living?					
FAQ 3a: Will I be able to return to my usual activities?					
Reduction in	✓	✓(mixed U-DBS and B-		NI	Based on retrospective analysis, all types of surgery improved functional

Evidence	MRgFUS	DBS	GK	Notes
functional outcomes		DBS)		outcomes when compared with baseline, but no differences were explored between treatments. When MRgFUS was compared with U-DBS in indirect comparison, no differences were found, only one study in prospective analysis showed that U-DBS is statistically significantly better than MRgFUS after 6 months follow-up.
FAQ 3b: Will I be able to return to work?				
No evidence found				
FAQ 3c: Will I be able to drive/return to driving?				
No evidence found				
FAQ 3d: Will my quality of life improve?				
Quality of life	✓	✓(B-DBS)	NI	Only comparison between MRgFUS and B-DBS was available. Both interventions improved all assessed outcomes related to quality of life significantly when compared to baseline, however, no differences were found between interventions.
FAQ 4: What are the possible adverse effects of treatment?				
FAQ 4a: What side effects might I experience from my treatment?				
Adverse events (procedural and <3mths)	NA	NA	NA	Available evidence was insufficient to make a meaningful comparison.
FAQ 4b: What long-term risks are associated with treatment?				
Adverse events (persistent and 12mths+)	NA	NA	NA	Available evidence was insufficient to make a meaningful comparison.
KEY				
-	No noticeable difference			
+	Statistically significantly better than baseline/sham (not compared with other type of surgery)			
✓	Statistically significantly better than other types of surgery (not compared with baseline/sham)			
✓	Statistically significantly better than baseline/sham, but not significantly better than other type of surgery			
✓	Statistically significantly better than baseline/sham and significantly better than other types of surgery			

Evidence	MRgFUS	DBS	GK	Notes
B-DBS = bilateral deep brain stimulation; CRST = clinical rating scale for tremor; DBS = deep brain stimulation; MRgFUS = Magnetic Resonance-Guided Focused Ultrasound thalamotomy; NA = not applicable; NI = no information; U-DBS = unilateral deep brain stimulation				

4.2 STRENGTHS, LIMITATIONS AND UNCERTAINTIES

There were several limitations associated with the evidence included in this review. Little information was found on non-invasive treatment. This could include a variety of different medications and those patients under consideration and eligible for invasive surgical treatment were usually drug refractory. To examine the effects and safety of drug therapies given the number of different medications available was beyond the scope of this review. Evidence was also limited for the GK intervention. The evidence included in this review mainly considered the comparison between MRgFUS and DBS, with very little information regarding the comparison between GK and MRgFUS and no information between GK and DBS. The Health Quality Ontario HTA 2018[1] reports that there is a shortage of long-term data on the effectiveness and safety of GK thalamotomy which is rarely used and so the report stated that is was not possible to make a recommendation on this procedure. However, the report authors stated that it may have a role in rare cases for example in elderly people who cannot undergo more invasive procedures such as DBS.

The main limitation of the evidence identified for the effectiveness and safety of the surgical options under consideration was the generally poor quality of the studies and in some cases the lack of long term data, particularly with MRgFUS which is a relatively new technique.[9] Although this review is based on the findings of guidelines, HTAs and systematic reviews, these usually included only observational studies with very often small sample sizes. Pooled estimates were often based on data from studies with very different study designs (RCTs, retrospective analyses, case series) and heterogeneity was repeatedly reported as an issue. Therefore, comparability of the effect estimates for the various interventions is questionable. Where GRADE was used to assess the evidence base for the findings of guidelines/HTAs the grading was usually low or very low. In a number of cases evidence was also taken from retrospective studies. However, individual case series studies have not been extracted for this report. Finally, studies included in the guidelines/HTA/systematic reviews were often in small populations of patients. This limits the overall quality of the evidence on which the findings of this review are based.

For tremor-dominant PD the PICO question was much narrower than for ET and only evidence on the effects on tremor based on RCTs was included if it compared HIFU with one of the other three treatments of interest. No information on how the respective interventions may affect the other motor symptoms usually associated with PD was extracted. Evidence for PD was based on a single RCT with only 27 patients comparing MRgFUS with Sham interventions. Though results tended to favour MRgFUS compared to sham for the effects on tremor any judgment of the balance of benefit and harm for the four treatments in tremor-dominant PD will be hampered by limitations mentioned.

This review is focused on the treatment of essential tremor and did not report on tremor associated with conditions other than ET and tremor-dominant PD. Where studies referred to patients with tremor with no further details as to the type or cause of the tremor they were excluded from this review.

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APPENDIX 1: SEARCH STRATEGIES

Summary of search results

Database	Date searched	Dates	Results
CDSR	10.10.19	Issue 10/12: Oct 2019	90
DARE	15.10.19	Up to 2015/03/31	108
HTA	15.10.19	up to 2018/03/31	49
KSR Evidence	10.10.19	up to 2019/10/10	156
Epistemonikos	10.10.19	up to 2019/10/10	158
NICE Guidance	15.10.19	2012-2019/10/15	2
ECRI Guidelines	15.10.19	up to 2019/10/15	8
NICE Evidence	15.10.19	2012-2019/10/15	326
GIN	15.10.19	up to 2019/10/15	1
Total			**898**
Total after de-duplication (2012-2019)			**420**

Search strategies

Cochrane Database of Systematic Reviews (CDSR) (Wiley): Issue 10 of 12, October 2019
Searched 10.10.19.19

#1 tremor*:ti,ab,kw 3656
#2 MeSH descriptor: [Essential Tremor] this term only 115
#3 MeSH descriptor: [Tremor] this term only 555
#4 (involuntary near/3 quiver*):ti,ab,kw 1
#5 #1 or #2 or #3 or #4 3656

CDSR = 89 records
Cochrane Protocols = 1 records

Epistemonikos (Internet): up to 2019/10/10
https://www.epistemonikos.org/
Searched 10.10.19.19

TITLE: (Familia* or hereditary or essential or heredofamilia* or heredo-familia* or juvenile or presenile or senile or benign or idiopathic or paralysis agitans or semirhythmic or semi-rhythmic or static or limb or limbs or muscle or muscles or muscular or neonatal or nerve or nerves or action or intention or coarse or continuous or darkness or fine or intermittent or involuntary or passive or passive or persistent or pillrolling or pill-rolling or resting or rest or perioral or peri-oral or saturnine) AND tremor*
OR
ABSTRACT: (Familia* or hereditary or essential or heredofamilia* or heredo-familia* or juvenile or presenile or senile or benign or idiopathic or paralysis agitans or semirhythmic or semi-rhythmic or static or limb or limbs or muscle or muscles or muscular or neonatal or nerve or nerves or action or intention or coarse or continuous or darkness or fine or intermittent or involuntary or passive or passive or persistent or pillrolling or pill-rolling or resting or rest or perioral or peri-oral or saturnine) AND tremor*
OR
TITLE: involuntary AND quiver*
OR

ABSTRACT: involuntary AND quiver*

Limited to Systematic Reviews only; not Cochrane SRs

N=158

KSR Evidence (Internet): up to 2019/10/10
http://www.ksrevidence.com
Searched 10.10.19.19
1 tremor* in All text 155
2 quiver or quivers in All text 1
3 #1 or #2 156

Database of Abstracts of Reviews of Effects (DARE) (CRD): up to 2015/03/31
Health Technology Assessment Database (HTA) (CRD): up to 2018/03/31
Searched 15.10.19.19
https://www.crd.york.ac.uk/CRDWeb/
1 (tremor*) IN DARE, HTA 131
2 MeSH DESCRIPTOR Essential Tremor EXPLODE ALL TREES 12
3 MeSH DESCRIPTOR Tremor EXPLODE ALL TREES 13
4 (involuntary NEAR quiver*) IN DARE, HTA 0
5 #1 OR #2 OR #3 OR #4 132
DARE = 108 records
HTA = 49 records

ECRI Institute Guidelines Trust (Internet): up to 2019/010/15
Searched 15.10.19.19
https://guidelines.ecri.org/
tremor* OR "involuntary quiver" OR "involuntary quivers"
n=7

Guidelines International Network (GIN) Library (Internet): up to 2019/010/15
Searched 15.10.19.19
http://www.g-i-n.net

Search terms	**Results**
tremor* OR "involuntary quiver" OR "involuntary quivers"	1
Total retrieved	**1**

NICE Evidence Search: limited to guidance and SRs only (Internet): up to 2019/010/15
Searched 15.10.19.19
https://www.evidence.nhs.uk/

Search terms	**Results (Guidance; Systematic Reviews, HTAs): 01/01/2015-15/10/2019**
tremor	326
"involuntary quiver"	0

"involuntary quivers"	0
Total retrieved	**326**

National Institute for Health and Care Excellence (NICE): Guidelines: up to 2019/10/15
Searched 15.10.19.19
https://www.nice.org.uk/

Searched all NICE Guidance, 01/2012-10/2019:

Search term	Result
Tremor	2
"involuntary quiver"	0
"involuntary quivers"	0
Total	**2**