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Systematic Review

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Systematic Review

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**Commissioned by the Austrian Ministry of Health**, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

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# Content

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## List of abbreviations

AE(s) .....adverse event(s)
ASSFN .....American Society of Stereotactic and Functional Neurosurgery
AWMF .....Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V.
BIRD.....Binational Industrial Research and Development
CE.....Conformité Européene
CG .....control group
CGb .....control group (bilateral deep brain stimulation)
CGDBS .....control group (deep brain stimulation)
CGRF.....control group (radiofrequency)
CGu .....control group (unilateral deep brain stimulation)
CRST.....Clinical Rating Scale for Tremor
CT.....computerised tomography
d.....day(s)
DBS .....deep brain stimulation
ET.....essential tremor
ET+ .....essential tremor plus
FAB .....Frontal Assessment Battery
FTM .....Fahn-Tolosa-Marin
FU(s) .....follow-up(s)
HRQoL .....health-related quality of life
ICD-10 .....International Statistical Classification of Diseases and Related Health Problems 10th Revision
IG.....intervention group
IQWiG.....Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care]
J. .....Jahre
LKF.....leistungsorientierte Krankenanstaltenfinanzierung
LQ .....Lebensqualität
m.....month(s)
MCID.....minimal clinically important difference
MeSH .....Medical Subject Headings
MMSE.....Mini Mental State Examination
MOCA ..... Montreal Cognitive Assessment
MR..... magnetic resonance
MRI..... magnetic resonance imaging
n ..... number of patients
n.s..... not statistically significant (p>0.05)
NHS ..... National Health Service
NICE ..... National Institute for Health and Care Excellence
NR..... not reported
NSH ..... National Health Service
Ö..... Österreich
ÖGN ..... Austrian Society of Neurology [Österreichische Gesellschaft für Neurologie]
PCSs ..... prospective cohort studies
PICO..... patient/population, intervention, comparison and outcomes
pts ..... patients
QoL ..... quality of life
QUEST ..... Quality of life in Essential Tremor Questionnaire
RCT ..... randomised controlled trial
red..... Reduction
RF ..... radiofrequency
RoB ..... risk of bias
ROBINS-I..... Risk Of Bias In Non-randomised Studies – of Interventions
s.s. ..... statistically significant
SAE(s)..... serious adverse event(s)
SD ..... standard deviation
tcMRgFUS ... transcranial MR-guided focused ultrasound system
UK..... United Kingdom
untersch. ..... unterschiedlich
US ..... United States
USA..... United States of America
v. ..... von
versch..... verschieden
VIM..... ventral intermediate
vs ..... versus
yrs..... years

# Executive Summary

## Introduction

### Health Problem

Essential tremor (ET) is one of the most prevalent movement disorders. Approximately 0.9% of people, or more than 60 million individuals worldwide, are affected. ET is a disabling disease, interfering significantly with quality of life. Although ET does not shorten life expectancy, it can impair daily living activities, thus leading to social embarrassment. Currently, ET is treated with occupational treatment, adaptation of coping strategies, and/or medications. Also, deep brain stimulation (DBS), a functional neurosurgical brain surgery, is offered for drug-resistant ET.

**essential tremor (ET): movement disorder with ~1 % affected people worldwide**

### Description of Technology

Transcranial magnetic resonance-guided high-intensity focused ultrasound (tcMRgFUS) is a thermal ablation technique that avoids the need for open brain surgery. TcMRgFUS combines high-intensity focused ultrasound with real-time magnetic resonance imaging (MRI). The ultrasound heats and destroys targeted tissue at the focal point of hundreds of ultrasound beams. The MRI allows visualisation of the ablation process. The claimed benefit of tcMRgFUS is being a non-invasive and incisionless technique for treating patients with ET. Therefore, tcMRgFUS avoids the need for open brain surgery.

**non-invasive, incisionless technique combining ultrasound with MRI destroying target tissue by heat**

This report aimed to investigate whether tcMRgFUS is more effective and safe compared to sham, DBS or radiofrequency (RF) thalamotomy in patients with drug-resistant ET.

**project aim: to assess efficacy and safety**

## Methods

The current review assessed two different patient groups: patients not eligible or not yet eligible for DBS (population A) and patients eligible for DBS (population B). For that purpose, a systematic literature search was conducted in December 2022. The following databases were searched, identifying a total of 467 hits: Medline via Ovid, Embase, The Cochrane Library, and HTA-INAHTA. Reference screening, study selection, data extraction and assessment of the quality of the included studies were performed by two independent researchers. Depending on the study design, the quality of studies was assessed using the 'Cochrane Risk of Bias (RoB) 2 tool', the 'Institute of Health Economics RoB checklist' (IHE-20), or the 'RoB In Non-randomised Studies – of Interventions' (ROBINS-I) tool. The strength of the critical efficacy and safety outcomes was rated according to Grading of Recommendations, Assessment, Development and Evaluations (GRADE).

**population A & B**

**systematic search**

**risk of bias assessment**

**GRADE rating**

### Domain effectiveness

Tremor severity was defined as *critical* to deriving a recommendation since it is the most relevant efficacy outcome for patients with ET.

**critical efficacy outcome**

### Domain safety

Adverse events (AEs) and serious adverse events (SAEs) were defined as most relevant to ET patients, thus, they are critical to deriving a recommendation.

**critical safety outcomes**

## Results

### Patients not eligible or not yet eligible for deep brain stimulation (population A)

*Available evidence*

**1 RCT and 2 prospective single-arm observational studies**

For population A, one RCT (with four follow-up (FU) publications) could be identified with some concerns of bias comparing tcMRgFUS to sham. Furthermore, two prospective single-arm observational studies were included for safety outcomes with low to moderate quality.

*Clinical effectiveness*

**statistically significant improved tremor severity, functional disability and health-related quality of life**

In the RCT (n=76), tremor severity was statistically significantly reduced in the tcMRgFUS group compared to the sham procedure at the 3-month FU assessed by the Clinical Rating Scale for Tremor (reduction by 47% vs 0.1%; from 18.1±4.8 to 9.6±5.1 vs from 16.0±4.4 to 15.8±4.9; $p<0.001$). Furthermore, functional disability (62% vs 3%) and health-related quality of life (46% vs 3%) statistically significantly improved.

*Safety*

**various adverse events and 1 serious adverse event**

Various AEs occurred at the 3-month FU; however, the authors did not report statistically significant between-group differences. Similar AEs were reported for the one-year non-comparative results of the RCT and the two non-comparative studies (n=35; n=40) (e.g. paresthesias, numbness, gait disturbance, head discomfort). One SAE (i.e. dense and permanent hypesthesia of the thumb and finger) occurred in one patient of the intervention group at one-year FU of the RCT.

### Patients eligible for deep brain stimulation (population B)

*Available evidence*

**2 retrospective comparative cohort studies**

For population B, two retrospective comparative cohort studies were identified with critical methodological quality. TcMRgFUS was compared to unilateral/bilateral DBS and RF thalamotomy.

*Clinical effectiveness*

**statistically significant improved tremor severity in 1 of 2 comparative studies**

In one of the cohort studies (n=73), tremor severity was statistically significantly reduced ($p<0.05$) in the tcMRgFUS group (from 54.9 to 17.7 points; 55.7% from baseline) compared to bilateral DBS (from 64.4 to 13.2 points; 79.5% from baseline) at the 12-month FU; however, not when compared to unilateral DBS (from 59.5 to 15.8 points; 62.8% from baseline). Based on a self-defined scale, the second cohort study (n=59) assessed tremor severity and revealed no statistically significant differences in treatment success at the 12-month FU among the three groups. However, more patients in the tcMRgFUS group met the predefined criteria of successful treatment compared to the DBS group. No statistically significant improvements in functional disability and health-related quality of life could be observed.

*Safety*

**less adverse events in the intervention than in the control groups**

In the first retrospective cohort study, the tcMRgFUS arm generally reported less neurologic, hardware-related, and haemorrhage AEs than in unilateral and bilateral DBS. In the second cohort study, less treatment-related complications were reported in the tcMRgFUS arm compared to DBS and RF thalamotomy. No SAEs were reported in both studies.

### Upcoming evidence

One ongoing RCT (JPRN-UMIN000010714), including ten patients, was revealed. It compares the efficacy and safety of tcMRgFUS to sham procedure in drug-resistant ET patients at 12 months. The planned primary outcome is tremor severity; the estimated completion date is not reported.

**1 ongoing RCT (n=10)**

### Reimbursement

In Austria, tcMRgFUS is currently not included in the catalogue of benefits, and hence, it is not a fully reimbursable service.

**Austria: tcMRgFUS is not reimbursed**

## Discussion

The existing evidence indicates that tcMRgFUS compared to sham procedure, may be more effective regarding tremor severity. Comparing tcMRgFUS to DBS or RF thalamotomy, evidence was inconclusive, showing that tremor severity statistically significantly improved in one of two studies. Evidence gaps concerning tcMRgFUS vs sham could be observed, such as the lack of comparative long-term data. In addition, more evidence of well-designed head-to-head RCTs comparing unilateral and bilateral tcMRgFUS to other therapies is needed.

**lack of comparative long-term data and well-designed head-to-head RCTs**

Moreover, the applicability of the results may be limiting as the included studies were conducted in various geographical regions where patients may have different disease characteristics at baseline.

**limiting applicability**

## Conclusion

The evidence indicates that tcMRgFUS is superior to sham procedure in terms of tremor severity, functional disability, and health-related quality of life at the 3-month FU period in patients with drug-resistant ET who are not eligible or not yet eligible for DBS (population A). Safety data indicate that tcMRgFUS may be a safe treatment option for this patient population.

**tcMRgFUS is more effective than sham procedure**

For patients eligible for DBS (population B), the evidence is insufficient to assess comparative efficacy and safety of tcMRgFUS due to the critical RoB and retrospective design of the studies. Randomised, well-conducted, comparative studies are needed, focusing on directive comparing tcMRgFUS in patients eligible for DBS and long-term safety in large registry-based studies.

**for patients eligible for DBS: insufficient evidence**

Based on the results of this assessment, we recommend reimbursing tcMRgFUS with restriction to patients who are not eligible or not yet eligible for DBS and limited to specialised clinical settings.

**recommendation with restriction**

# Zusammenfassung

## Einleitung

### Indikation und therapeutisches Ziel

**essentieller Tremor: häufige Bewegungsstörung**

**schränkt Lebensqualität ein**

**weltweit ~1 % betroffen**

**verschiedene Behandlungsmöglichkeiten**

Essentieller Tremor zählt zu den häufigsten Bewegungsstörungen. Weltweit sind etwa 0,9 % oder mehr als 60 Millionen Menschen betroffen. Bei Personen über 65 Jahren lag die Prävalenz sogar bei 5,8 %. Essentieller Tremor kann zu Zittern, Gangstörungen und sozialen Beeinträchtigungen führen und die Lebensqualität erheblich einschränken. Obwohl essentieller Tremor die Lebenserwartung nicht verkürzt, kann er Aktivitäten des täglichen Lebens beeinträchtigen und so zu sozialer Scham führen. Die klinische Diagnose basiert auf den klassischen Symptomen und Tremormerkmalen, welche durch Anamnese und körperliche Untersuchungen ermittelt werden. Gegenwärtig wird medikamentenresistenter essentieller Tremor mit Ergotherapie, Anpassungs- und Bewältigungsstrategien und/oder Medikamenten behandelt. Auch die tiefe Hirnstimulation, ein minimalinvasiver, neurochirurgischer Eingriff, um ein umschriebenes Kerngebiet im Gehirn elektrisch zu stimulieren, wird für medikamentenresistenten essentiellen Tremor angeboten.

### Beschreibung der Technologie

**tcMRgFUS: nicht-invasive, schnittfreie Technik, die Ultraschall mit MRT kombiniert und das Zielgewebe durch Hitze zerstört**

Transkranielle magnetresonanzgesteuerte hochintensive fokussierte Ultraschalltherapie (tcMRgFUS) ist eine thermische Ablationstechnik, die eine Operation am Gehirn überflüssig macht. TcMRgFUS kombiniert hochintensiven fokussierten Ultraschall mit Echtzeit-Magnetresonanztomographie (MRT). Mittels Ultraschall wird das Zielgewebe von Hunderten von Ultraschallstrahlen erhitzt und verödet. Die MRT ermöglicht die Visualisierung des Abtragungsprozesses. Die Kombination von Echtzeit-Bildführung mit der fokussierten Gewebeablation ermöglicht eine Kontrolle durch kontinuierliche Überwachung der Gewebetemperatur. Der erwartete Vorteil von tcMRgFUS ist, dass es sich um eine nicht-invasive und schnittfreie Technik zur Behandlung von Patient*innen mit essentiellem Tremor handelt. Daher kann mit tcMRgFUS eine Gehirnoperation vermieden werden.

### Fragestellung

**Projektziel: Wirksamkeit und Sicherheit von tcMRgFUS**

**Bewertung zu zweier Populationen**

Ziel der vorliegenden Arbeit war es, die Evidenz zur klinischen Wirksamkeit und Sicherheit von tcMRgFUS im Vergleich zu Scheinbehandlung, tiefer Hirnstimulation oder Radiofrequenz-Thalamotomie bei Patient*innen mit essentiellem Tremor zu untersuchen. Die Bewertung erfolgte zu zwei Patient*innengruppen: Patient*innen, die nicht oder noch nicht für eine tiefe Hirnstimulation in Frage kommen (Population A) und Patient*innen, die für eine tiefe Hirnstimulation in Frage kommen (Population B).

## Methoden

**systematische Suche**

**Bewertung des Verzerrungsrisikos; GRADE-Bewertung**

Dafür wurde im Dezember 2022 eine systematische Literatursuche durchgeführt. Die Suche wurde in vier Datenbanken Medline über Ovid, Embase, The Cochrane Library und der INAHTA Database durchgeführt und ergab insgesamt 467 Treffer. Das Screening der Studien, die Studienauswahl, Datenextraktion und Bewertung der methodischen Qualität der eingeschlossenen Studien wurden von zwei unabhängigen Autor*innen durchgeführt. Je

nach Studiendesign wurde die Qualität der Studien anhand des „Cochrane Risk of Bias (RoB) 2“ Tools, der „Institute of Health Economics RoB Checkliste“ (IHE-20) oder des „RoB In Non-randomised Studies – of Interventions“ (ROBINS-I)“ Tools bewertet. Die Qualität der Evidenz der entscheidungsrelevanten Wirksamkeits- und Sicherheitsendpunkte wurde nach der GRADE-Methode (Grading of Recommendations, Assessment, Development and Evaluations) bewertet.

### Klinische Wirksamkeit

Der Schweregrad von Tremor wurde als entscheidend für die Ableitung einer Empfehlung definiert, da er der wichtigste Endpunkt für die Wirksamkeit bei Patient*innen mit essentiellem Tremor ist.

**entscheidungsrelevanter Wirksamkeitsendpunkt**

### Sicherheit

Unerwünschte Ereignisse und schwerwiegende unerwünschte Ereignisse wurden als besonders relevant für Patient*innen mit essentiellem Tremor definiert und sind daher entscheidend für die Ableitung einer Empfehlung.

**entscheidungsrelevante Sicherheitsendpunkte**

## Ergebnisse

Fünf Studien (9 Publikationen) wurden in die vorliegende systematische Übersichtsarbeit einbezogen.

**5 Studien eingeschlossen**

### Patient*innen, die nicht oder noch nicht für eine tiefe Hirnstimulation in Frage kommen (Population A)

#### *Verfügbare Evidenz*

Für die Population A wurde eine randomisierte kontrollierte Studie (mit vier Nachbeobachtungspublikationen) ausgewählt, in welcher tcMRgFUS mit Scheinbehandlung verglichen wurde. Die Qualität der Evidenz wurde als moderat eingestuft. Für den Endpunkt Sicherheit wurden zusätzlich zwei prospektive einarmige Beobachtungsstudien mit geringer bis mäßiger Qualität einbezogen.

**1 randomisierte kontrollierte Studie und 2 prospektive einarmige Beobachtungsstudien**

#### *Klinische Wirksamkeit*

In der randomisierten kontrollierten Studie (n=76) war der Schweregrad von Tremor in der Interventionsgruppe im Vergleich zur Scheinbehandlung nach der dreimonatigen Nachbeobachtung statistisch signifikant reduziert, gemessen anhand der „Clinical Rating Scale for Tremor“ (Reduktion von 47 % vs. 0,1 %; von 18,1±4,8 auf 9,6±5,1 Punkte vs. von 16,0±4,4 auf 15,8±4,9 Punkte; $p<0.001$). Auch eine statistisch signifikante Verbesserung der funktionellen Beeinträchtigung (62 % vs. 3 %) und gesundheitsbezogenen Lebensqualität (46 % vs. 3 %) konnte festgestellt werden.

**statistisch signifikante Verbesserung von Tremor, funktioneller Beeinträchtigung und gesundheitsbezogener Lebensqualität**

#### *Sicherheit*

In der randomisierten kontrollierten Studie traten bei der dreimonatigen Nachbeobachtung zahlreiche unerwünschte Ereignisse auf. Die Studienautor*innen berichteten jedoch nicht über statistisch signifikante Unterschiede zwischen den Gruppen. Für die nicht vergleichenden Ergebnisse der Nachbeobachtungen der randomisierten kontrollierten Studie und der beiden nicht vergleichenden Studien (n=35; n=40) wurden nach einem Jahr ähnliche schwerwiegende unerwünschte Ereignisse gemeldet wie z. B. Sensibilitätsstörung, Taubheitsgefühl, Gangstörung, Kopfbeschwerden. Ein schwerwiegendes

**zahlreiche unerwünschte Ereignisse und 1 schwerwiegendes unerwünschtes Ereignis**

unerwünschtes Ereignis, d. h. ein dauerhaftes Taubheitsgefühl des Daumens und des Fingers, trat bei einer Person in der Interventionsgruppe nach einem Jahr Nachbeobachtungszeitraum in der randomisierten kontrollierten Studie auf.

### Patient*innen, die für eine tiefe Hirnstimulation in Frage kommen (Population B)

*Verfügbare Evidenz*

**2 retrospektive vergleichende Kohortenstudien**

Für die Population B wurden zwei retrospektive vergleichende Kohortenstudien identifiziert. TcMRgFUS wurde mit unilateraler und bilateraler tiefer Hirnstimulation und Radiofrequenz-Thalamotomie verglichen. Die Qualität der Evidenz wurde als kritisch bewertet.

*Klinische Wirksamkeit*

**statistisch signifikante Verbesserung von Tremor in 1 von 2 vergleichenden Studien**

**keine statistisch signifikanten Verbesserungen der funktionellen Beeinträchtigung und Lebensqualität**

In der ersten Kohortenstudie (n=73) war der Schweregrad von Tremor in der Interventionsgruppe (55,7 % Reduktion ab Ersttestung; von 54,9 auf 17,7 Punkte) im Vergleich zu bilateraler tiefer Hirnstimulation (von 64,4 auf 13,2 Punkte; 79,5 % Reduktion ab Ersttestung) bei der zwölfmonatigen Nachbeobachtung statistisch signifikant reduziert ($p<0,05$), jedoch nicht im Vergleich zur unilateralen tiefen Hirnstimulation (62,8 % Reduktion ab Ersttestung; von 59,5 auf 15,8 Punkte). Die zweite Kohortenstudie (n=59) bewertete den Schweregrad von Tremor anhand einer selbstdefinierten Skala und ergab keine statistisch signifikanten Unterschiede im Behandlungserfolg nach zwölf Monaten Nachbeobachtung zwischen den drei Gruppen (tcMRgFUS vs. tiefe Hirnstimulation vs. Radiofrequenz-Thalamotomie). Allerdings erfüllten in der Interventionsgruppe mehr Patient*innen die vordefinierten Kriterien für eine erfolgreiche Behandlung als in der Gruppe der tiefen Hirnstimulation. Es konnten keine statistisch signifikaten Verbesserungen hinsichtlich der funktionellen Beeinträchtigung und der gesundheitsbezogenen Lebensqualität beobachtete werden.

*Sicherheit*

**in der Interventionsgruppe weniger unerwünschte Ereignisse als in den Kontrollgruppen**

In der ersten retrospektiven Kohortenstudie wurden in der Interventionsgruppe weniger neurologische, gerätebedingte und blutungsbedingte schwerwiegende unerwünschte Ereignisse berichtet als bei der unilateralen und bilateralen tiefen Hirnstimulation. In der zweiten Kohortenstudie wurden in der Interventionsgruppe weniger behandlungsbedingte Komplikationen dokumentiert als bei der tiefen Hirnstimulation und der Radiofrequenz-Thalamotomie.

### Laufende Studien

**1 laufende randomisierte kontrollierte Studie (n=10)**

Eine laufende randomisierte kontrollierte Studie (JPRN-UMIN000010714), die zehn Patient*innen umfasst, wurde identifiziert. Sie vergleicht die Wirksamkeit und Sicherheit von tcMRgFUS mit Scheinbehandlung bei medikamentenresistenten Patient*innen mit essentiellem Tremor nach zwölf Monaten. Der geplante primäre Endpunkt ist der Schweregrad von Tremor; das voraussichtliche Abschlussdatum wurde nicht angegeben.

### Kostenerstattung

**in Österreich wird tcMRgFUS nicht erstattet**

In Österreich ist tcMRgFUS derzeit nicht im Leistungskatalog (LKF, Leistungsorientierte Krankenanstaltenfinanzierung) enthalten und somit keine voll erstattungsfähige Leistung.

## Diskussion

**je nach Population unterschiedliche Ergebnisse hisichtlich Effektivität und Sicherheit**

Die vorliegende Evidenz deutet darauf hin, dass tcMRgFUS bei Patient*innen mit medikamentenresistentem essentiellem Tremor im Vergleich zu Scheinbehandlung hinsichtlich des Schweregrades von Tremor, der funktionellen Beeinträchtigung und der gesundheitsbezogenen Lebensqualität wirksamer sein könnte (1 RCT mit vier Nachbeobachtungspublikationen; n=76). Im Vergleich von tcMRgFUS mit tiefer Hirnstimulation oder Radiofrequenz-Thalamotomie gab es uneindeutige Ergebnisse, die zeigten, dass sich der Schweregrad von Tremor in einer von zwei Studien statistisch signifikant verbesserte. Die Sicherheitsdaten deuten darauf hin, dass tcMRgFUS eine sichere Behandlungsoption für diese Patient*innengruppe darstellen könnte. Es gab jedoch Lücken in der Evidenz etwa das Fehlen von vergleichenden Langzeitdaten. Mehr Evidenz aus gut konzipierte randomisierte kontrollierte Studien wird benötigt, die tcMRgFUS mit anderen Therapien vergleicht und welche sich auf die langfristige Sicherheit konzentriert.

**weitere Evidenz mit vergleichenden Langzeitdaten und gut konzipierten randomisierten kontrollierten Studien erforderlich**

**Übertragbarkeit möglicherweise eingeschränkt**

Die Übertragbarkeit der Ergebnisse ist möglicherweise eingeschränkt, da die eingeschlossenen Studien in verschiedenen geografischen Regionen durchgeführt wurden, in denen die Patient*innen zu Beginn der Studie unterschiedliche Krankheitsmerkmale aufwiesen.

## Schlussfolgerung und Empfehlung

**Population A: tcMRgFUS ist wirksamer als Scheinbehandlung**

Für Patient*innen, die nicht oder noch nicht für eine tiefe Hirnstimulation in Frage kommen (Population A), deutet die derzeitige Evidenz darauf hin, dass die bewertete Technologie tcMRgFUS gleich sicher und effektiver in Bezug auf den Schweregrad von Tremor, die funktionelle Beeinträchtigung und gesundheitsbezogene Lebensqualität bei Patient*innen mit medikamentenresistentem essentiellem Tremor ist als die Vergleichsgruppe der Scheinbehandlung. Allerdings ist eine vergleichende Langzeitevidenz erforderlich.

**Population B: unzureichende Evidenz**

Bei Patient*innen, die für eine tiefe Hirnstimulation in Frage kommen (Population B), ist die Evidenz für eine vergleichende Bewertung der Wirksamkeit und Sicherheit von tcMRgFUS aufgrund der retrospektiven Studiendesigns und des hohen Verzerrungsrisikos unzureichend.

**Empfehlung mit Einschränkung**

Aufgrund der vorliegenden Evidenz empfehlen wir, die Erstattung von tcMRgFUS auf Patient*innen, die für eine tiefe Hirnstimu-lation nicht oder noch nicht in Frage kommen und auf spezialisierte klinische Einrichtungen zu beschränken.

# 1 Background

## 1.1 Overview of the disease, health condition and target population

### Overview of essential tremor[1]

Tremor as a symptom is defined as a rhythmic, involuntary, and oscillatory movement of a body part, regarding the recent tremor classification [1, 2]. In 2018, a consensus statement was defined with two axes based on clinical characteristics and aetiology (see Chapter 1.2). Importantly, tremor syndromes are classified only according to clinical features (axis 1) [2, 3]. In this classification, essential tremor (ET) is defined as "an isolated tremor syndrome of bilateral upper limb action tremor that occurs with at least 3 years' duration, with or without tremor in other locations and the absence of other neurological signs, such as dystonia, ataxia or parkinsonism" [3].

**Tremor: Bewegungsstörung mit rhythmischer, unwillkürlicher und zeitlich schwankender Bewegung; Essentieller Tremor (ET): basierend auf klinischen Merkmalen und Ursachen**

According to the Consensus Statement 2018 on tremor disorders by the International Parkinson and Movement Disorder Society, ET has been established as a heterogeneous disorder [4]. Combinations of different activation conditions of tremor syndromes exist. Rest, posture and kinetic are the positions most accentuating the tremor, allowing a syndromic approach for a precise classification [1]. *Rest tremors* occur in a relaxed body part, which is entirely supported against gravity. *Action tremors* occur with the muscle's voluntary contraction; they can be subdivided into postural (e.g. arm elevation), isometric (e.g. making a fist), and kinetic (e.g. voluntary movements) tremors. ET, a symmetric tremor, is an action tremor and most obvious in the hands and wrists; it can also affect the lower extremities, head and voice. It can be further described as a postural, kinetic (i.e. body part is moving), and also as sporadic resting tremor [5]. However, for ET, postural tremor is the most common syndrome [1], which is present while maintaining a position against gravity [5].

**verschiedene Aktivierungsbedingungen von Tremorsyndromen**

**ET: meist symmetrischer Aktions- und Haltetremor**

The natural course of ET caused by a neurological disease is a progressive increase in tremor severity over time. Tremor increases in amplitude, becomes more disabling and may spread to involve other body regions [6]. Throughout the disease course, factors associated with disease progression and rates of disease progression may vary. The two most important factors associated with disease progression and capturing the degree of asymmetrical disease are i) asymmetrical self-reported tremor onset and ii) asymmetrical tremor ratings at the first clinic visit. These two variables are associated with an increased rate of tremor severity over time. Generally, small to moderate asymmetry is common in ET, with an increased severity on the non-dominant side [7].[2]

**natürlicher, progressiver Krankheitsverlauf mit Zunahme des Schweregrades**

[1] **A0007** – What is essential tremor in this assessment? &
**A0002** – What is essential tremor in the scope of this assessment?

[2] **A0004** – What is the natural course of essential tremor?

## Burden of disease for patients with essential tremor[3]

**Komorbiditäten z. B. Bluthochdruck, Störungen v. Nervensystem, Fettstoffwechsel, Gang, Kognition und Psyche**

A wide range of comorbidities and symptoms exist [4]. The most common comorbidities are other nervous system disorders, hypertension, lipid metabolism and mood/anxiety disorders [3]. ET may lead to intention tremors (i.e. during purposeful/voluntary movements), gait impairments (particularly gait ataxia), disability and social handicaps and may impair quality of life (QoL) [4]. Furthermore, hearing impairments, sleep disorders, and cognitive deficits (particularly executive functioning) are reported [3].

**Einschränkungen zu Hause und in der Arbeit**

**psychosoziale Beschwerden**

ET is disabling in the home and workplace, interfering significantly with QoL, functional activities, and social interaction. Although ET does not shorten life expectancy, it can impair writing, eating, drinking, reading, and concentration, thus leading to social embarrassment [8]. Up to 25% of ET patients retire early or modify their career path. It is also important to mention that 30-50% of those initially diagnosed with ET eventually receive an additional tremor diagnosis or a different diagnosis after further evaluation. However, physical and psychosocial complaints such as stigmatisation, depression and social isolation due to tremor should impact therapeutic decision-making [5].[4]

**lebenslanges, fortschreitendes Syndrom**

**untersch. subjektive Wahrnehmung**

ET is a lifelong progressive syndrome where patients may have different demands and problems based on age and gender. The subjective perception of this impairment is extremely variable within patients. Therefore, it is crucial to know about the spectrum of manifestations of this condition and how to measure tremor severity and complaints as the coping strategies differ. The treatment selection critically depends on the knowledge of the subjective complaints [1].

## Target population[5]

**häufige Bewegungsstörung mit weltweit ca. 1 % Betroffenen**

ET is one of the most prevalent movement disorders (apart from restless leg syndrome [8]) and one of the most common tremor syndromes [1, 9], next to enhanced physiologic tremor and parkinsonian tremor [5]. Worldwide, approximately 0.9% of people [4] or more than 60 million individuals, are affected by ET [3]. In an update on ET's worldwide prevalence published in 2021, the pooled prevalence (all ages) was calculated by 1.3% [10]. Similarly, the European Academy of Neurology estimates the prevalence to be 1% [11]. However, for individuals over 65 years, the prevalence was 5.8% [10].

**leicht steigender Anstieg in UK und Frankreich**

In the United Kingdom (UK) and France, slightly increasing trends were shown: higher incidences among males and a significant increase with age. The yearly average crude incidence rate (per 100,000 person-years) was 18.2 in the UK and 21.4 in France [12].

**mehr Männer als Frauen betroffen**

Males and females can be affected, but the complaints may differ. For men, the association of hand tremor severity with midline tremor (i.e. jaw, voice, or neck) is stronger than for women. Women's likelihood of being affected by impairing head and/or voice tremors (additionally to hand tremor) is increased [1].

[3] **A0005** – What is the burden of disease for patients with essential tremor?

[4] **A0006** – What are the consequences of essential tremor for the society?

[5] **A0023** – How many people belong to the target population (essential tremor)?

The prevalence increases with advancing age, where the prevalence estimate in people aged under 20 years was 0.04% and 2.9% in elderly aged 80 years and above. Interestingly, there is a peak of affected people in the second and sixth decades [4]. Most ET patients do not have treatment until 60 to 69 years of age because it tends to progress slowly [5].

**mehr ältere als junge Betroffene**

Figure 1-1 [3] presents the prevalence of ET in 15 countries based on studies from 2001 to 2021. Crude prevalence estimates are based on studies in populations with varying age structures and methodologies.

**Prävalenz in 15 Ländern**

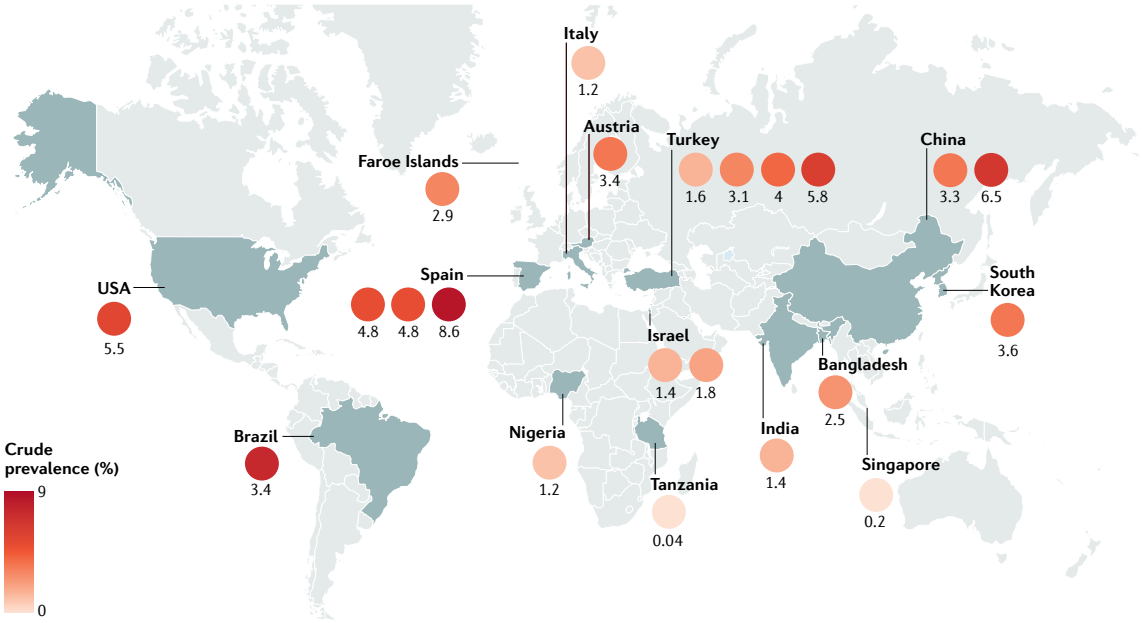



*Figure 1-1: Prevalence of essential tremor based on studies from 2001–2021 [3]*

## Genetic and environmental risk factors[6]

A family history of tremor or neurologic disease suggests that genetic components play a role in ET aetiology [5]. 50–70% of ET patients have a positive family history. In some families, inheritance seems to follow an autosomal dominant pattern with incomplete penetrance, although the inheritance pattern varies. Some family members of ET patients may also have other movement disorders (e.g. parkinsonism, dystonia) [3].

**bei 50-70 % Familiengeschichte als Risikofaktor**

Non-genetic risk factors also play an aetiological role in some ET patients. These factors include diet, lifetime and occupational exposures to pesticides, farming and exposure to heavy metals. Furthermore, shorter sleep duration is suggested to have an association with an increased risk of incident ET [3].

**nicht-genetische Faktoren wie z. B. Ernährung, Schlaf und Pestizide spielen eine ätiologische Rolle**

[6] **A0003** – What are the known risk factors for essential tremor?

## 1.2 Current clinical practice[7, 8]

**klinische Diagnose basierend auf Tremorsymptomen aus Anamnese und körperlicher Untersuchung**

ET's clinical diagnosis is based on classic symptoms and tremor features obtained from medical history and physical examination. ET patients typically have no other neurologic findings. Thus, after careful differential diagnosis, ET is sometimes considered a diagnosis of exclusion. First, the tremor is categorised based on its activation condition (i.e. resting, kinetic/intention, postural, isometric tremor), topographic distribution, and frequency [5]. Two major approaches exist to diagnose and manage ET.

**klinische Beschreibung zur syndromalen Klassifizierung des Tremors**

The first axis, *clinical description*, includes tremor characteristics, historical features, laboratory tests, and associated signs, which allows a syndromic classification based on these descriptors. Other neurologic symptoms (e.g., Parkinson's syndrome, cerebellar disease, peripheral neuropathy) must be absent.

**ET+: zusätzlich zu ET-Merkmalen leichte, unklare, neurologische Anzeichen, welche für Diagnose nicht ausreichen**

Patients often have slight symptoms, which are not sufficient to allow a diagnosis but are suspicious. These patients are defined as having ‚essential tremor plus (ET+)' [1]. In the 2018 Consensus Statement, ET+ is defined as "tremor with the characteristics of ET and additional neurological signs of uncertain significance such as impaired tandem gait, questionable dystonic posturing, memory impairment, or other mild neurological signs of unknown significance that do not suffice to make an additional syndrome classification or diagnosis [2, 3]."

**Ursachenprüfung**

In the second axis, *aetiology* needs to be checked if there is a diagnosis of ET- or ET+ syndrome. This second axis might be hypoglycaemia, hyperthyroidism, and medication-induced tremor, which need to be excluded with lab tests and medical history. However, most patients with ET- or ET+ syndromes will have no identifiable cause, and causal treatments are recommended only if a treatable aetiology is found [1].

The two axes to diagnose and manage ET are summarised in Figure 1-2 (adapted from [2]).

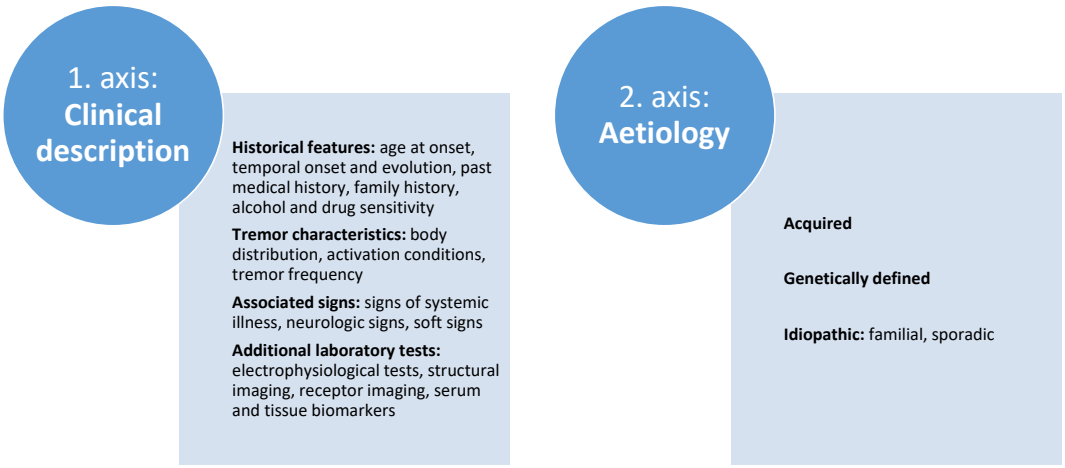



*Figure 1-2: Two axes to diagnose and manage essential tremor (adapted from [2])*

[7] **A0024** – How is essential tremor currently diagnosed according to published guidelines and in practice?

[8] **A0025** – How is essential tremor currently managed according to published guidelines and in practice?

## Clinical guidelines[8]

**AWMF Guideline S2k 2022:**

**medikamentöse Behandlung**

Tremor can sometimes be treated with, e.g. occupational treatment or adaptation of coping strategy [1]. According to the German **AWMF guideline S2k**[9] (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V.) published in 2022, *medical treatment* with propranolol, primidone and topiramate is recommended (⇑⇑ strength of consensus 100%). The current evidence does not allow separate therapy recommendations for the subgroups of young or elderly patients. The Austrian Society of Neurology (ÖGN, Österreichische Gesellschaft für Neurologie) participated in this guideline [13].

**Tiefe Hirnstimulation: unilateral vs. bilateral**

Next to these first-line drugs, ET patients can be treated by *deep brain stimulation (DBS)*, a functional neurosurgical technique [1]. According to the AWMF guideline S2k, *unilateral* DBS of the thalamus should be offered to severely affected patients with drug-resistant ET (⇑ strength of consensus 100%). *Bilateral* DBS of the thalamus should be provided to severely affected ET patients or ET patients with severe axial tremor (voice tremor or head tremor) if the symptoms are drug-resistant (⇑ strength of consensus 100%). The clarification of the individual indication is reserved for specialised centres [13].

**unilaterale transkranielle MRT-gesteuerte hochintensive fokussierte Ultraschalltherapie (tcMRgFUS)**

As recommended by the AWMF guideline S2k, the *unilateral transcranial magnetic resonance-guided high-intensity focused ultrasound* (tcMRgFUS) treatment should be offered to patients with drug-resistant ET if unilateral treatment is promising and/or an improvement in the patient's QoL can be assumed despite only unilateral tremor reduction (⇑ strength of consensus 100%). The determination of the individual indication is left to specialised centres. According to the guideline, *bilateral* tcMRgFUS cannot be considered due to a lack of evidence and previous experience of severe side effects (⇔ strength of consensus 92%) [13].

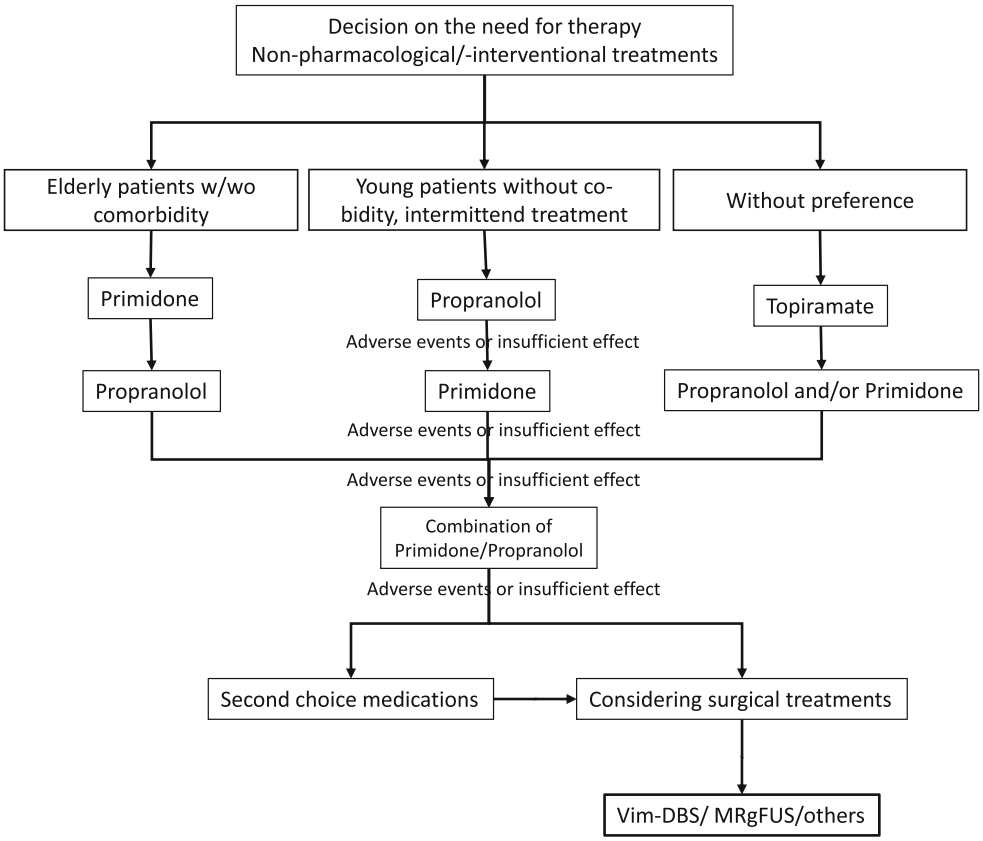
**Radiofrequenz-Thalamotomie nicht empfohlen**

*Unilateral thalamotomy with radiofrequency* (RF) lesions should no longer be used except when methods with fewer side effects are not feasible in justified exceptional cases and in specialised centres (⇓ strength of consensus 100%). *Bilateral* thalamotomy with RF lesions should not be used at all (⇓⇓ strength of consensus 100%) [13].

**Entscheidungsbaum für ET-Behandlung**

The following Figure 1-3 presents a decision tree for treating patients with ET in a German centre [1].

[9] Formal consensus-building has taken place.




*Abbreviations: DBS – deep brain stimulation. MRgFUS – magnetic resonance-guided high-intensity focused ultrasound. VIM – ventral intermediate nucleus of the thalamus. w/wo – with/without.*

*Figure 1-3: Decision tree for the treatment of patients with essential tremor [1]*

## 1.3 Features of the intervention

**"schnittfreie" Technik kombiniert MRT mit Ultraschall unter Anwendung von Hitze, wodurch Zielgewebe zerstört wird**

Transcranial magnetic resonance-guided high-intensity focused ultrasound (TcMRgFUS) is an incisionless thermal ablation technique. It avoids the need for open brain surgery and physically traversing brain tissue on the trajectory towards the ventral intermediate (VIM) nucleus of the thalamus with an RF probe. TcMRgFUS combines high-intensity focused *ultrasound* with real-time magnetic resonance imaging *(MRI)*. The ultrasound heats and destroys targeted tissue at the focal point of hundreds of ultrasound beams. The MRI allows visualisation of the ablation process using thermographic imaging superimposed on patient-specific anatomy. The combination of real-time image guidance with the focused ablative technology allows control by continuously monitoring the tissue temperature [8].[10, 11, 12]

[10] **B0002** – What is the claimed benefit of transcranial magnetic resonance-guided high-intensity focused ultrasound treatment in relation to the comparators?

[11] **A0001** – For which health conditions, and for what purposes is transcranial magnetic resonance-guided high-intensity focused ultrasound treatment used?

[12] **B0001** – What is the technology (transcranial magnetic resonance-guided high-intensity focused ultrasound treatment) and the comparator(s)?

According to the manufacturer (InSightec Ltd., Haifa, Israel), the device is intended for thermal ablation of targets in the i) thalamus, ii) sub thalamus and iii) pallidum regions of the brain. For that purpose, thermal-focused ultrasound energy under full MR planning and thermal imaging control is used to treat i) ET, ii) idiopathic Parkinson's disease (unilateral treatments), and iii) neuropathic pain.[10, 13]

**Verwendung für ET, Parkinson und neuropathische Schmerzen**

Exablate 4000 is commercialised in Europe (i.e. Denmark, Finland, France, Germany, Italy, Netherlands, Poland, Portugal, Spain, Sweden, Switzerland, and the UK (as of November 2022).[14]

**Exablate 4000 wird in versch. europäischen Ländern vermarktet**

To date, more than 10,000 patients have been treated with ExAblate 4000 worldwide. More than 130 centres offer tcMRgFUS treatment worldwide, including 31 in Europe. According to the submitting Austrian hospital, in 2021, no tcMRgFUS was performed. It is forecasted that the annual frequency at Austrian institutions would be 150 treatments, whereof 80 treatments would be performed at the submitting Austrian hospital [14].[15]

**weltweit: mehr als 10.000 Behandlungen in 130 Zentren**

**Ö: ca. 150 Behandlungen/ Jahr**

## Features of the comparators

Next to tcMRgFUS, DBS or RF thalamotomy are used in treating ET. *DBS* is a functional neurosurgical brain surgery. Here, a permanent electrode with four to eight contacts is implanted in the VIM nucleus of the thalamus with stereotactic planning of the target with/without confirming the target area with microelectrodes in the awake patient. The stimulator is implanted subcutaneously, and an also subcutaneously implanted wire connects to the electrode. The current applied through the permanent electrode contacts blocks fibres and cells in the target area [1].[12]

**Tiefe Hirnstimulation: neurochirurgische Technik mit implantierten Elektroden**

*RF lesioning* of the VIM thalamus has almost been abandoned when DBS became available in the 1990s. This open brain surgery is a functional neurosurgical technique. It is performed with an electrode through which a high-frequency current produces local heating of the tissue at the electrode's tip above 60°, destroying all cells and fibre tracts in the target region. The patient's head must be connected to a frame. Imaging of the head and frame using computerised tomography (CT) or MRI allows for defining the target coordinates where the electrode is placed with high-precision instruments. The duration and strength of the electrical current determine the lesion's extent. Afterwards, the heating electrode is removed. However, RF lesioning is only rarely conducted if a focused ultrasound or DBS is not possible [1].[12]

**Radiofrequenz-Thalamotomie: neurochirurgische Technik wobei mittels Strom über Elektrode Hitze Zielgewebe zerstört**

Compared to DBS and RF thalamotomy, the claimed benefit of tcMRgFUS is its non-invasive, non-surgical and incisionless thermal ablation technique for treating patients with ET. Therefore, tcMRgFUS avoids the need for open brain surgery. It further combines high-intensity focused ultrasound with real-time MRI.[10] The following Table 1-1 presents the features of the intervention and comparators.

**Vorteil von tcMRgFUS: "schnittfreies", nicht-invasives Verfahren in Kombination mit MRT und Ultraschall**

[13] **A0020** – For which indications has transcranial magnetic resonance-guided high-intensity focused ultrasound treatment received marketing authorisation or CE marking?

[14] **B0003** – What is the phase of development and implementation of transcranial magnetic resonance-guided high-intensity focused ultrasound treatment and the comparator(s)?

[15] **A0011** – How much are transcranial magnetic resonance-guided high-intensity focused ultrasound treatments utilised?

*Table 1-1: Features of the intervention and comparators*

| | Intervention/Technology | Comparators (reference codes in catalogue of benefits) |
|---|---|---|
| Name | Exablate 4000 (type 1.0 and 1.1) | Deep brain stimulation (AH030, AH031, AH040, AH041) and radiofrequency thalamotomy (AA160[16]) |
| Proprietary name | - | |
| Manufacturer | InSightec Ltd. | |
| Names in other countries | - | |
| Reference codes | 3902589CE01 | |
| Class/GMDN code | - | |

## Administration, tools and personnel required and supplies needed to use transcranial magnetic resonance-guided high-intensity focused ultrasound treatment

**strukturelle und personelle Anforderungen**

According to information provided by the submitting hospital [14], a tcMRg-FUS system, MRI pressure infusion unit, and invasive pressure module are needed as structural requirements. Furthermore, personnel requirements such as neurosurgeons, anaesthetists, neurologists, nursing, and medical, therapeutic and diagnostic health professions need to be available.[17, 18]

**Systemkomponenten, Betriebsspezifikationen, Softwarefunktionen und technische Anforderungen**

System components, operational specifications, and software features are needed, as well as technical requirements.[19, 20] System components include a helmet system, storage transfer cart, front-end unit, operator console, stereotactic frame, equipment cabinet, and cooling unit. As operational specifications, a focused ultrasound transducer system is used, which is a helmet-shaped phased array transducer that can be controlled individually to refocus the ultrasound beams to a common focal point.

## Regulatory & reimbursement status

**2012: CE-Zertifizierung**

**in Ö keine Kostenrückerstattung**

The technology Exablate 4000 tcMRgFUS (type 1.0 and 1.1) received a Conformité Européene (CE) mark in December 2012. The technology is commercialised in Europe (i.e. Denmark, Finland, France, Germany, Italy, Netherlands, Poland, Portugal, Spain, Sweden, Switzerland, and the UK). In Austria, tcMRgFUS is currently not included in the catalogue of benefits (LKF, Leistungsorientierte Krankenanstaltenfinanzierung), and hence, it is not a fully reimbursable service.[21]

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16 This is the reference code for 'thalamotomy'.

17 **B0004** – Who administers transcranial magnetic resonance-guided high-intensity focused ultrasound treatment and the comparators and in what context and level of care are they provided?

18 **B0008** – What kind of special premises are needed to use transcranial magnetic resonance-guided high-intensity focused ultrasound treatment and the comparator(s)?

19 Exablate Neuro data sheet from Insightec: see https://dwdntcdfjp7dx.cloudfront.net/wp-content/uploads/2021/08/Exablate-Neuro-Platform-Datasheet-PUB41004616-NA-Rev1.pdf (access date 19/01/2023)

20 **B0009** – What supplies are needed to use transcranial magnetic resonance-guided high-intensity focused ultrasound treatment and the comparator(s)?

21 **A0021** – What is the reimbursement status of transcranial magnetic resonance-guided high-intensity focused ultrasound treatment?

# 2 Objectives and Scope

## 2.1 PICO question

**PIKO-Frage**

Is tcMRgFUS treatment in comparison to *sham, placebo, no treatment, DBS or RF thalamotomy* in patients with *drug-resistant essential tremor* more effective and safe concerning tremor severity, functional disability, health-related QoL, global assessment of the disease symptoms, length of hospital stay as well as (serious) adverse events?

## 2.2 Inclusion criteria

**Einschlusskriterien für relevante Studien**

Inclusion criteria for relevant studies are summarised in Table 2-1.

*Table 2-1: Inclusion criteria*

| | |
|---|---|
| **P**opulation | Patients (female/male, ≥18 years) with **drug-resistant**[22] **essential tremor**[23]<br>■ *Population A:* patients not eligible or not yet eligible for deep brain stimulation<br>■ *Population B:* patients eligible for deep brain stimulation<br>MeSH-terms: Essential Tremor<br>ICD-10 code: G25.0 Essential Tremor<br>*Source: informed by AWMF guideline S2k 2022 [13]* |
| **I**ntervention | **Transcranial** magnetic resonance-guided **high-intensity focused ultrasound** treatment ((tc-)MRgFUS or tc-HIFU)<br>Unilateral **focused ultrasound thalamotomy** |
| **C**ontrol | *Population A: tc*MRgFUS vs **sham, placebo, no treatment**<br>*Population B: tc*MRgFUS vs **deep brain stimulation, radiofrequency thalamotomy**<br>*Rationale: informed by Institute for Quality and Efficiency in Health Care (IQWiG) report 2021 [16] and AWMF guideline S2k 2022 [13]* |
| **O**utcomes | |
| Efficacy | Tremor severity (e.g. CRST[24])<br>Functional disability (e.g. CRST)<br>Health-related quality of life (e.g. QUEST[25])<br>Global assessment[26] of the disease symptoms (e.g. CRST)<br>Length of hospital stay<br>*Rationale: informed by IQWiG report 2021 [16] and National Institute for Health and Care Excellence (NICE) guidance 2018 [18]* |

[22] Defined as „tremor that was refractory to at least two trials of medical therapy, including at least one first-line agent (propranolol, primidon)“ [15].

[23] Studies with mixed populations were only included, if outcomes were reported separately.

[24] Clinical Rating Scale for Tremor

[25] Quality of Life in Essential Tremor Questionnaire

[26] The global assessment is a part of the CRST rated by the examiner and patient (0=no functional disability to 4=severe disability). “This subjective global severity is based on the assessment of tremor-related disability, which is calculated according to the percent of impairment in carrying out all activities of daily living and the cosmetic effect of tremor. The global assessment can serve as the ‘gold standard’ for validating this clinical rating scale” [17].

| | |
|---|---|
| Safety | Adverse events (AEs)<br>Serious adverse events (SAEs) |
| **S**tudy design | |
| Efficacy | Randomised controlled trials<br>Prospective/Retrospective comparative cohort studies |
| Safety | Randomised controlled trials<br>Prospective/Retrospective comparative cohort studies<br>Prospective non-comparative observational studies (>20 patients enrolled)[27] |
| Search period | Inception to 2022 |

[27] Prospective non-controlled observational studies were included for populations A and B.

# 3 Methods

## 3.1 Research questions

**EUnetHTA Core Model®**

Assessment elements from the European Network for Health Technology Assessment (EUnetHTA) Core Model® for the production of Rapid Relative Effectiveness Assessments (Version 4.2) were customised to the specific objectives of this assessment [19].

## 3.2 Clinical efficacy and safety

### 3.2.1 Systematic literature search

**systematische Literatursuche in 4 Datenbanken**

The systematic literature search was conducted on the 20th and 21st of December 2022 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- HTA-INAHTA

The systematic search was limited to articles published in English or German. After deduplication, overall, 467 citations were included. The specific search strategy employed can be found in the Appendix (Chapter Literature search strategies).

**Suche nach laufenden Studien**

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on the 24th of January 2023, resulting in one potentially relevant hit (see Appendix Table A-10).

**insgesamt 9 Publikationen (5 Studien) identifiziert**

The product's manufacturer, InSightec Ltd. (Exablate 4000 transcranial MR guided focused ultrasound system), submitted 13 publications, of which no new citations were identified. No additional study was found by hand-search, resulting in nine hits (5 studies).

### 3.2.2 Flow chart of study selection

**Literaturauswahl**

Overall, 467 hits were identified. Two independent researchers (LG, GG) screened the references, and in case of disagreement, a third researcher was involved in solving the differences. The selection process is displayed in Figure 3-1.

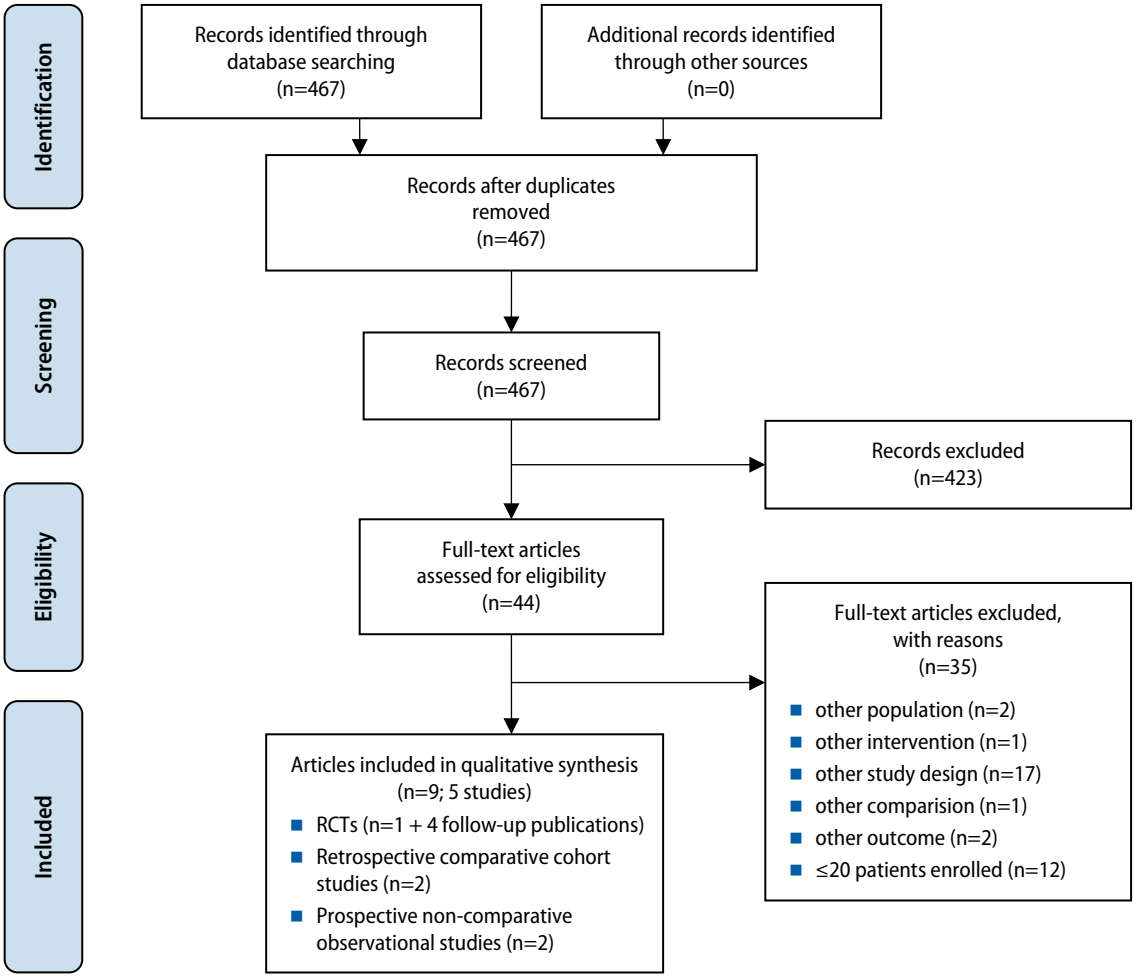


*Figure 3-1: Flow chart of study selection (PRISMA Flow Diagram)*

### 3.2.3 Analysis

**Datenextraktion und Kontrolle**

The data from five studies (in nine publications) were systematically extracted into data extraction tables (see Appendix Table A-1 to Table A-3). The single-data extraction method with verification by another researcher was used: One researcher (LG or RF) extracted the data, and one further researcher (GG) controlled the extracted data. No further data processing (e.g., indirect comparison) was applied.

**Bewertung von Studienqualität und Verzerrungsrisiko**

Three independent researchers (LG, RF, GG) critically appraised the five included studies. The studies were systematically assessed for internal validity and risk of bias (RoB). The 'Cochrane Collaboration's tool' version 2 [20] and the 'Institute of Health Economics (IHE) RoB checklist' [21] were used for assessing the RoB for the RCT and non-comparative studies, respectively (see Appendix Table A-4 and Table A-6). For the comparative cohort studies, the Risk Of Bias In Non-randomised Studies – of Interventions (ROBINS-I) assessment tool [22] was used, as presented in Appendix Table A-5. Disagreements were solved through consensus.

**Details zu IHE Checkliste**

For the 'IHE RoB checklist', overall, the RoB was assessed using a predefined point score (range: 0-20, Table 3-1): Higher scores indicate a low RoB, and lower scores indicate a high RoB. Detailed thresholds are presented in Table 3-2.

*Table 3-1: Overall risk of bias point scores for risk of bias assessment of case series*

| Answers to specific questions of the IHE checklist | Points |
|---|---|
| No | **0** |
| Partial | **0.5** |
| Unclear | **0.5** |
| Yes | **1** |

*Table 3-2: Cut-off criteria for the risk of bias assessment of overall risk of bias of case series*

| Criteria | Points |
|---|---|
| Low risk | **> 18** |
| Moderate risk | **14.5 to 18** |
| High risk | **≤ 14** |

Two independent researchers (LG, RF) rated the strength of evidence according to the GRADE schema [19] for each critical efficacy and safety outcomes individually. In case of disagreement, a third researcher (GG) was involved in solving the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [23].

### 3.2.4 Synthesis

**Evidenzsynthese mittels GRADE**

Based on data extraction tables (see Appendix Table A-1 to Table A-3), data on each selected critical outcome category were synthesised across studies according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) [23]. The research questions were answered in plain text format with reference to GRADE evidence tables included in Appendix Table A-7 and Table A-8; results were summarised in Table 5-1 and Table 5-2.

# 4 Results: Clinical efficacy and Safety

## 4.1 Outcomes

### 4.1.1 Outcomes efficacy

**entscheidungsrelevante Wirksamkeitsendpunkte**

In accordance with a consulted clinical expert, the following efficacy outcome was defined as most relevant to patients with ET. Therefore, this outcome was defined as *critical* to derive a recommendation:

- Tremor severity (measured by CRST)

**weitere wichtige Endpunkte**

Further efficacy outcomes were defined as *important* but not critical to derive a recommendation:

- Functional disability (measured by CRST, Frontal Assessment Battery (FAB))
- Health-related quality of life (measured by QUEST)
- Global assessment[26] of the disease symptoms (measured by CRST)
- Length of hospital stay

#### Clinical Rating Scale for Tremor

**klinische Bewertungsskala für Tremor (Teile A, B, C)**

The Clinical Rating Scale for Tremor (CRST) is a validated tool to assess the severity of tremor, and it is specifically designed for ET. This tool [24] includes three parts (A, B, and C), whereof each part yields a subtotal score that can be combined for a total score [17]. *Part A* assesses the whole body tremor severity considering anatomical locations (9 body parts) in three situations of rest, maintaining postures and performing activities. Tremor severity in each of these nine body parts is rated by amplitude. *Part B* assesses the impact of tremor on motor tasks, particularly pouring liquids and writing, so-called action tremors of the upper extremities. Tremor severity is determined by watching the patient carry out these activities. *Part C* assesses the tremor-related functional disability of patients. These items evaluate tremor severity with speaking, bringing liquids to the mouth, eating, dressing, hygienic care, working, and domestic tasks [17].

**höhere Werte: stärkerer Tremor bzw. mehr Einschränkung**

The maximum possible scores are 80 (part A), 36 (part B), and 28 (part C), making a maximum possible total score (parts A, B, and C) of 144 points [17, 25]. Higher scores indicate more severe tremor and greater disability [15]. No values for minimal clinically important differences (MCID) could be found.

#### Quality of life in Essential Tremor Questionnaire

**Fragebogen zur Lebensqualität (LQ) bei ET (5 Domänen)**

The Quality of life in Essential Tremor Questionnaire (QUEST), a patient self-reported questionnaire, measures tremor symptom interference with daily living activities [26]. It is composed of 30 items and is divided into five domains: speaking, work and finance, hobbies and leisure activities, physical activity, and psychological aspects. The QUEST quantifies the affect of tremor on QoL based on independence in daily living, social inclusion, emotional well-being, and employability [26, 27]. Each scale expresses its scores as a percentage of the total possible score; lower scores indicate greater satisfaction with the QoL domain assessed. Evaluation of the internal consistency of

**niedrigere Werte: größere Zufriedenheit mit LQ**

the scales supports the validity of the QUEST. Reliability was excellent for the whole instrument [28]. MCID threshold values for the overall ET population were found. The summary index of the QUEST was divided into three patient-rated global impressions of improvement overall MCID: a little better (minimal improvement): overall MCID -4.47; the same (no change): overall MCID -0.05; and a little worse (minimal worsening): overall MCID 4.98 [29].

#### Frontal Assessment Battery

**Frontal Assessment Battery bewertet exekutive Funktionen**

**höhere Werte: bessere Funktionen**

The Frontal Assessment Battery (FAB) is used to assess executive functions located in the frontal lobes. It investigates the conceptualisation processes, motor programming, abstract reasoning, mental flexibility, executive control, resistance to interference, environmental autonomy and inhibitory control. The total possible score is 18 points; scores ≥12 are considered normal [27]. Therefore, higher scores indicate better function. The FAB has good convergent, concurrent and discriminant validity with fair internal consistency. However, this was assessed only in early cognitively impaired patients [30]. No values for minimal clinically important differences (MCID) could be found.

### 4.1.2 Outcomes safety

**entscheidungsrelevante Sicherheitsendpunkte**

The following safety outcomes were defined as most relevant to patients with ET. Therefore, these outcomes were defined as *critical* to derive a recommendation:

- Adverse events (AEs)
- Serious adverse events (SAEs)

## 4.2 Included studies

Study characteristics and results of all included studies are displayed in the Appendix Table A-1 to Table A-3 and in the evidence profiles in Table A-7 and Table A-8.

### 4.2.1 Included studies efficacy

#### Study and patient characteristics

##### TcMRgFUS vs sham procedure (population A)

**1 RCT mit Cross-Over und 4 Nachbeobachtungsstudien bis zu 5 Jahren (J.):**

One double-blinded, multicentre RCT was identified according to the PICO question [15]. In the study protocol, a crossover RCT was planned. In the publication, it is reported as a 'normal' RCT. However, there was a cross over from the sham to the tcMRgFUS group. It was conducted in the United States, Canada, Japan, and South Korea and served as a primary analysis with an up to one-year FU [15]. Further four articles could be identified following-up this RCT: Chang 2018 (2-year FU post treatment) [31], Halpern 2019 (3-year FU) [32], Park 2019 (4-year FU) [33], Cosgrove 2022 (5-year FU) [34]. The critical outcome tremor severity was reported as the primary outcome measure [15].

TcMRgFUS was compared to sham procedure in 81 patients with drug-resistant ET, whereof 76 patients were randomised into a 3:1 ratio; analysing 56 patients in the intervention group (IG) and 20 in the control group (CG). 21 ET patients (i.e. unblinded cohort) were treated with tcMRgFUS after the 3-month blinded assessment period (19 assigned to the CG who crossed over to tcMRgFUS and two assigned to tcMRgFUS in whom the procedure was incomplete). There was no loss to FU for the between-group comparison at three months. Comparative data were only reported at the 3-month FU [15].

**tcMRgFUS vs. Scheinbehandlung**
**76 Patient*innen (Pts.)**
**kontrollierte Daten *nur* bei 3 Monaten Nachbeobachtung**

Inclusion criteria were postural or intention tremor of the hand that was moderate to severe and disabling tremor, drug-resistant tremor to at least two attempts with medical therapy, and stable medication dose of concurrent medical therapy for 30 days before randomisation. The sponsor of this trial were InSightec (manufacturer of the intervention), Focused Ultrasound Foundation, and Binational Industrial Research and Development (BIRD) Foundation [15].

**Einschlusskriterien**
**Sponsoren u. a. InSightec**

The mean age among the analysed cohort (n=76) was 71 years, and the majority were males (68%) and right-handed (83%). Disease duration was, on average, 17 years. No comorbidities were reported [15] (see Appendix Table A-1).

**Ø 71 J.,**
**17 J. Krankeitsdauer,**
**68 % Männer**

### TcMRgFUS vs deep brain stimulation or radiofrequency thalamotomy (population B)

Two retrospective comparative three-arm cohort studies from the US [35] and South Korea [36] were included in the analysis comparing tcMRgFUS with either bilateral or unilateral thalamic DBS [35] and RF thalamotomy or DBS [36]. The study duration was between 2004 to 2013 [35] and 1995 to 2014 [36]. No sponsors were funding the study [35], and funding was not reported in the second study [36]. Both studies did not state any primary outcome [35, 36].

**2 vergleichende Kohortenstudien: tcMRgFUS vs. Tiefe Hirnstimulation/ Radiofrequenz-Thalamotomie**

59 [36] and 85 [35] patients with drug-resistant ET were enrolled in these studies, and 59 [36] and 73 [35] patients were analysed. There was a loss to follow-up (FU) of 12 patients (14%) in one study [35] and no loss in the other study [36]. Inclusion criteria were drug-resistant ET in both studies with preoperative and postoperative evaluation using the CRST and QUEST [35] or a record of efficacy and treatment-related complications [36]. FUs were at 12 months [36] or, on average, at 12 (tcMRgFUS group) and 13 months (CGs) [35] post treatment.

**59-85 Pts.**
**12-13 Monate Nachbeobachtungszeitraum**

The patients were between 63 [36] and 72 [35] years old, and in both studies, more (53 and 87%) males were included. The mean disease duration ranges between 14 and 21 years in the three groups [36] but was not reported in the other study [35]. 62-86% of patients were right-handed [35], but the other study did not report on that [36]. Both studies did not report comorbidities (see Appendix Table A-2).

**Ø 63-72 J., 14-21 Monate Nachbeobachtungszeitraum**

**53-87 % Männer**

### 4.2.2 Additional included studies safety

#### Study and patient characteristics

**2 nicht-vergleichende Beobachtungsstudien: 35-60 Pts. 55 % der Pts. mit ET (1 Studie)**

**Sponsor: InSightec (1 Studie)**

For safety, two additional prospective, non-comparative studies (multi- [26] and single-centred [27]) from Japan [26] and Italy [27] were included in the analysis. TcMRgFUS was assessed in 35 [26] and 60 [27] enrolled patients. In one study, all patients were diagnosed with ET [26], whereas, in the other study, only 55% had ET [27]. 35 [26] and 40 [27] patients were analysed. Therefore, a loss to FU of 20 (33%) patients occurred [27], but no loss in the other study [26]. The study duration was between 2015 to 2016 [26]. One study was supported by InSightec [26], whereas the other study had no sponsors [27]. The critical outcome tremor severity was reported as the primary outcome measure in one study [26], whereas the other study did not state any primary outcome [27]. The analysed non-comparative studies included both patient populations of interest (i.e. population A: patients not eligible or not yet eligible for deep brain stimulation; population B: patients eligible for deep brain stimulation).

**Einschlusskriterien 6-12 Monate Nachbeobachtungszeitraum**

Inclusion criteria were ≥22 years old, diagnosis of moderate to severe disabling postural or intentional tremor in the dominant upper extremity, drug-resistant tremor, and medication doses were required to have been stable with no changes [26]. In the other study, patients had to be ≥18 years old and be willing to return for protocol-required FU visits but did not report inclusion criteria [27]. FU was between six [27] and 12 [26] months.

**Ø 70-71 J., 9-24 J. Krankheitsdauer, 77 % Männer**

The mean age of patients ranges between 70 [27] and 71 [26] years. 77% were male [26]; however, the other study did not report the gender of patients [27]. The mean disease duration was 13 [27] and was not reported in the other study [26]; however, the disease duration from initial symptoms was 24 years and nine years from initial diagnosis [26]. 97% of patients were right-handed [26], whereas the other study did not report on that [27]. No comorbidities were reported in both studies (see Appendix Table A-3.

## 4.3 Results

### 4.3.1 TcMRgFUS vs sham procedure (population A)

#### Tremor severity

**1 RCT: statistisch signifikante (s.s.) Verbesserung v. Tremor um 47 % im Vergleich zu 0,1 % (Scheinbehandlung)**

The *critical* outcome **tremor severity** was reported in the RCT (n=76) [15] as the primary outcome assessed using the CRST. Hand tremor severity was reduced by 47% in the unilateral tcMRgFUS group compared to 0.1% in the CG receiving a sham procedure at the 3-month FU (from 18.1±4.8 to 9.6±5.1) vs 0.1% (from 16.0±4.4 to 15.8±4.9; mean CRST change score of between-group difference). This difference was statistically significant ($p<0.001$). A further statistically significant difference ($p<0.001$) was found when comparing CRST scores between tcMRgFUS and sham group, with mean reductions of 41% (from 50.1 to 29.6) and 2% (from 44.1 to 43.1; p-value not reported; mean CRST change score of total score), respectively. After the 3-month FU, 19 out of 20 patients in the unilateral tcMRgFUS crossed over to the sham procedure, resulting in one cohort (n=70) that received unilateral tcMRgFUS. All one-year FU results and the FU publications are reported for the unilateral tcMRgFUS as non-comparative results [15].

At the one-year FU, the reduction in the hand tremor, which is assessed by the mean CRST change score, slightly decreased by 40% (n=70) (p<0.001). Similarly, the mean CRST change score (total score) was reduced by 35% (p-value is not reported) [15]. A statistically significant reduction in hand tremor based on the mean CRST change score persisted at two years; 56% (n=67), three years; 56% (n=52), four years; 56%; (n=12), five years; 73% (n=40). None of the FU publications reported the scores: mean CRST change and absolute changes [31-34].

**Handtremor bis zu 5 J. verbessert**

### Functional disability[28, 29]

The *important* outcome **functional disability** was reported in the RCT as a secondary outcome [15].

Functional disability or disability according to the CRST, which refers to part C, was statistically significantly reduced from baseline in the unilateral tcMRgFUS group 62% (from 16.5 to 6.2) compared to 3% (from 16.0 to 15.6) in the sham group (p<0.001) at three months analysis in the RCT (n=76) [15].

**s.s. Verbesserung der funktionellen Beeinträchtigung um 62 % vs. 3 %**

### Health-related quality of life[30]

The *important* outcome **health-related quality of life (HRQoL)** was reported in the RCT as another secondary outcome [15].

HRQoL was measured in the RCT using the Quality of Life in Essential Tremor (QUEST)[31]. At three months, the RCT (n=76) reported a statistically significant improvement from baseline in the QUEST score with a reduction of 46% (from 42.6 to 23.1) in the unilateral tcMRgFUS compared to 3% (42.8 to 41.4) in the sham procedure (p<0.001) [15].

**s.s. Verbesserung d. LQ um 46 % vs. 3 %**

### Global assessment of the disease symptoms

No evidence was found to answer the research question.

**keine Evidenz**

### Length of hospital stay

No evidence was found to answer the research question.

**keine Evidenz**

[28] **D0011** – What is the effect of transcranial magnetic resonance-guided high-intensity focused ultrasound treatment on patients' body functions?

[29] **D0016** – How does the use of transcranial magnetic resonance-guided high-intensity focused ultrasound treatment affect activities of daily living?

[30] **D0013** – What is the effect of transcranial magnetic resonance-guided high-intensity focused ultrasound treatment on disease-specific quality of life?

[31] A 30-item scale developed specifically for patients with ET, with higher score indicates worse quality of life.

### 4.3.2 TcMRgFUS vs deep brain stimulation or radiofrequency thalamotomy (population B)

#### Tremor severity

**2 vergleichende Studien:**

The *critical* outcome **tremor severity** was reported in two comparative cohort studies.

**s.s. Verbesserung v. Tremor nur im Vergleich zu bilateraler Tiefen Hirnstimulation**

One of the cohort studies (n=73), which compared unilateral tcMRgFUS to uni- or bilateral DBS [35], reported tremor severity based on CRST total score (parts A, B, and C), and observed tremor was assessed by CRST part A. The unilateral tcMRgFUS group (from 54.9 to 17.7 points; 55.7% from baseline) had a statistically significant reduction in CRST total score ($p<0.05$) compared to bilateral DBS (from 64.4 to 13.2 points; 79.5% from baseline) but not to unilateral DBS (from 59.5 to 15.8 points; 62.8% from baseline).

**s.s. Verbesserung im Endpunkt „beobachteter Tremor"**

Additionally, the unilateral tcMRgFUS group (from 13.4 to 8.7 points; 35.1% to baseline) had a statistically significant reduction in the outcome observed tremor ($p<0.05$) compared to bilateral DBS (from 22.1 to 3.8 points; 82.8% from baseline) but not to unilateral DBS (from 19.1 to 8.4 points; 56.0% from baseline) [35].

**keine s.s. Verbesserung v. Tremor**

Unilateral tcMRgFUS was compared to DBS or RF thalamotomy in the other cohort study (n=59) [36]. The tremor severity was assessed based on a self-defined scale[32] at one and 12 month(s) FU durations. At one month's assessment, 91.3% of the patients in the tcMRgFUS group, 89.5% in the DBS, and 100% in the RF thalamotomy met the predefined criteria of successful treatment. However, no statistically significant differences in treatment success were detected among the three groups ($p=0.54$). Noteworthy, successful treatment decreased at the 12-month assessment to 78.3% in tcMRgFUS, 84.25% in DBS, and 70.6% in the RF thalamotomy group with no statistically significant differences between groups ($p=0.62$) [36].

#### Functional disability[28, 29]

The *important* outcome **functional disability** was reported only in one of the two included cohort studies [35].

**keine s.s. Verbesserung der funktionellen Beeinträchtigung ...**

Functional disability was assessed based on part C of the CRST. The results showed no statistically significant difference in disabilities between unilateral tcMRgFUS at 12[33] months and bilateral DBS at 13 months ($p=0.59$) [35].

[32] Patient response (symptomatic efficacy) was categorised according to a disease-specific rating scale. Absent: complete tremor remission; Occasional: tremor persisted in a milder form (≥90% abolition); Partial: some improvement (≥50% abolition): No improvement: no improvement (<50% abolition). Ratings of 'absence' or 'occasional' indicated successful treatment.

[33] Except for 1 patient who only had a 3-month FU.

### Health-related quality of life[30]

The *important* outcome **HRQoL**[34] was reported only in one of the two included cohort studies [35].

HRQoL was measured in the cohort study (n=73) using the Quality of Life in Essential Tremor (QUEST).[35, 36] No statistically significant difference was found when comparing tcMRgFUS with bilateral DBS at 12[34] and 13 months, respectively [35].

**... und LQ**

### Global assessment of the disease symptoms

No evidence was found to answer the research question.

**keine Evidenz**

### Length of hospital stay

No evidence was found to answer the research question.

**keine Evidenz**

## 4.3.3 Patient safety

Full descriptions of reported AEs and SAEs for all studies and FUs are listed in Table A-1 to Table A-3.

### TcMRgFUS vs sham procedure[37, 38] (population A)

For the evaluation of (comparative) safety of tcMRgFUS compared to sham procedure in patients with drug-resistant ET who are not eligible or not yet eligible for DBS, one RCT was considered. Comparative data are only assessed at the 3-month FU for AEs, but not for SAEs. Long-term FU data are non-comparative, combining both patients from the initial IG and CG. Statistical significance between arms was not reported for secondary outcomes, including safety [15]. Furthermore, two non-comparative studies were identified [26, 27].

**1 RCT und 2 nicht-vergleichende Studien**

#### Adverse events

In the RCT (n=76), numerous AEs occurred in both groups during the 3-month FU period. Viewed inversely, *no* adverse event occurred in none of the patients of the tcMRgFUS but in eight patients (40%) of the sham group. Generally, more AEs were reported in the tcMRgFUS arm compared to the sham arm. Frequently occurring AEs were, among others, paresthesias or numbness at any region: 14 patients (25%) vs one (5%); gait disturbance[39]:

**1 RCT: unerwünschte Ereignisse nach 3 Monaten z. B. Taubheitsgefühl, Gangstörungen, Gliederdysmetrie, Gleichgewichtsstörungen**

[34] HRQoL data was analysed for tcMRgFUS and bilateral DBS only.

[35] A 30-item scale was developed specifically for patients with ET, with a higher score indicating worse quality of life.

[36] QUEST is a validated and a disease specific questionnaire.

[37] **C0008** – How safe is transcranial magnetic resonance-guided high-intensity focused ultrasound treatment in comparison to the comparator(s)?

[38] **C0007** – Are transcranial magnetic resonance-guided high-intensity focused ultrasound treatment and comparator(s) associated with user-dependent harms?

[39] Gait disturbances include any, objective, or subjective.

nine patients (16%) vs one (5%); limb dysmetria: five patients (9%) vs zero (0%); and disequilibrium sensation: three patients (5%) vs zero (0%). The authors did not report statistically significant between-group differences [15].

**mehr intraprozedurale Ereignisse in Kontrollgruppe**

On the other hand, more intraprocedural sensations or events were reported in the sham arm than in the tcMRgFUS arm; pin-site pain, oedema, or bruising[40]: zero (0%) vs seven patients (35%); nausea: zero (0%) vs two patients (10%); anxiety: zero (0%) vs two patients (10%); scalp tingling: zero (0%) vs one patient (5%); and back pain: zero (0%) vs one patient (5%) [15].

**intraprozedurale Ereignisse wie z. B. Kopfbeschwerden, Schwindel, Übelkeit, Rückenschmerzen**

Many AEs were reported for the non-comparative results of the RCT (total number of patients during 12 months), such as paresthesias or numbness at any region: 21 patients (38%); gait disturbances[39]: 20 patients (36%); headache[41]: eight patients (14%); limb dysmetria: seven patients (12%); and disequilibrium sensation: five patients (9%). Furthermore, intraprocedural sensations or events were reported (total number of patients); head discomfort[42]: 17 patients (30%); pin-site pain, oedema, or bruising: 17 patients (30%); vertigo/dizzy: 12 patients (21%); nausea: 11 patients (20%); scalp tingling: four patients (7%); and back pain: five patients (9%). On the other hand, only six patients (11%) reported no adverse events. In Appendix Table A-1, one can find a complete list of all AEs relating to both comparative 3-month FU and long-term FU events relating to all patients [15].

**2 nicht-vergleichende Studien: z. B. Gangstörung, Taubheitsgefühl, Lähmung**

Two non-comparative studies (n=35 [26]; n=40 [27]) assessed AEs after six [27] and 12 [26] months. The most frequently[43] reported AEs were gait disturbances: eight patients (23%); numbness/tingling: six patients (17%); unsteady gait: five patients (14%); hemiparesis: five patients (14%); hypotonia: three patients (9%); and dysarthria: three patients (9%). It is noteworthy that 77% of AEs were resolved within the first month [26].

**thalamotomiebedingte und gerätebezogene Komplikationen**

Thalamotomy-related complications were reported as contralateral weakness in three patients (8%), dysgeusia in one patient (3%), and gait instability in one patient (3%). On the other hand, MRI/ultrasound-related AEs such as dizziness 22%, scalp burning 16%, and nausea 8% were reported most often [27].

### Serious adverse events

**1 RCT: schwerwiegende unerwünschte Ereignisse (Sensibilitätsstörung)**

In the RCT, serious adverse events (SAEs) were neither reported in the IG (intervention group) nor the CG within the 3-month FU period. Within the long-term FU of up to one year, non-comparative data were reported: One patient (2%) suffered from dense and permanent hypesthesia of the dominant thumb and index finger, classified as an SAE by the RCT [15].

**2 nicht-vergleichende Studien: keine aufgetreten**

SAEs were reported in both non-comparative studies, but did not occur [26, 27].

[40] Pin-site pain, oedeme, or bruising attributable to placement of the stereotactic frame.

[41] Headache that lasted for >1 day

[42] Head discomfort descried either as heat or pressure.

[43] The most frequent AEs which were reported in ≥3 patients.

## TcMRgFUS vs deep brain stimulation or radiofrequency thalamotomy[37, 38] (population B)

**2 vergleichende und 2 nicht-vergleichende Studien**

For the evaluation of tcMRgFUS compared to DBS or RF thalamotomy in patients with drug-resistant ET who are eligible for DBS, two comparative cohort studies were identified assessing AEs 12 months post treatment. Both comparative studies did not report statistically significant differences [35, 36]. Furthermore, two non-comparative studies were identified [26, 27].

### Adverse events

**1/2 vergleichende Studie: neurologische, physische und hardwarebedingte Ereignisse, Blutungen**

In one of the included cohort studies (n=73) that compared unilateral tcMRgFUS with either unilateral or bilateral DBS, AEs were reported until the 3-month FU and at the 12-month FU. AEs are presented per treatment arm and categorised into four categories: neurologic, physical, haemorrhage, and hardware-related. The tcMRgFUS arm generally reported less neurologic, hardware-related, and haemorrhage AEs than both DBS groups. The results of this study are reported only as numbers of events [35].

**neurologische Ereignisse: Sensibilitäts-, Sprechstörungen, Schwäche**

**Neurologic AEs:** In unilateral tcMRgFUS (n=15), 14 paresthesias, one dysarthria, and one weakness were reported at the 3-month FU. Whereas only three paresthesia AEs were reported at 12 months. In the unilateral DBS arm (n=13), at three months, 11 gait disturbances and four AEs (paresthesia, dysarthria, weakness, and mental status change, respectively) were reported; in contrast, at 12 months, only two events of paresthesia were reported. Expectedly, more AEs were reported in the bilateral DBS arm (n=57): dysarthria (n=10), gait instability (n=10), weakness (n=4), and mental status change events (n=3) were reported at three months. Nevertheless, less AEs were reported at 12 months, with six dysarthrias, three mental status changes, one paresthesia, and one weakness event [35].

**physische Ereignisse: Schwindel, Kopfschmerzen, Übelkeit**

**Physical AEs (brief intraprocedural symptoms):** Physical AEs were reported only in the unilateral tcMRgFUS arm (n=15) and only at three months: lightheaded/dizzy (n=11), headache (n=9), nausea/vomiting (n=8), and flushed warmth events (n=4) [35].

**Blutungen bei Tiefer Hirnstimulation**

**Haemorrhage:** Two haemorrhages were reported only at three months in the bilateral DBS arm (n=57) [35].

**hardwarebedingte Ereignisse: MRT-Verbrennungen**

**Hardware-related AEs:** This category included infection, lead erosion, and MRI burn at the frame. In the unilateral tcMRgFUS arm (n=15), two MRI burns at the frame were reported at the 3-month FU. In the bilateral DBS arm (n=57), a total of three lead erosion events were reported, one at three months and two at 12 months. Additionally, one infection was reported at 12 months [35].

**1/2 vergleichende Studie: tendenziell weniger behandlungsbedingte Komplikationen in tcMRgFUS-Gruppe**

The second retrospective cohort study compared unilateral tcMRgFUS to DBS or RF thalamotomy (n=59). This study reported only treatment-related complications at one and 12 months. Generally, less treatment-related complications were reported in the unilateral tcMRgFUS arm compared to DBS and RF thalamotomy. However, at one month, less treatment-related complications occurred in the unilateral tcMRgFUS arm (13%, n=3) than in RF thalamotomy (59%, n=10), but more than in DBS (5%, n=1). However, at the 12-month FU period, treatment-related complications were reported less in tcMRgFUS (4%, n=1) than in RF thalamotomy (12%, n=2) and in DBS (21%, n=4) [36].

**2 nicht-vergleichende Studien: z. B. Gangstörung, Taubheitsgefühl, Lähmung**

Two non-comparative studies (n=35 [26]; n=40 [27]) assessed AEs after six [27] and 12 [26] months. The most frequently[43] reported AEs were gait disturbances: eight patients (23%); numbness/tingling: six patients (17%); unsteady gait: five patients (14%); hemiparesis: five patients (14%); hypotonia: three patients (9%); and dysarthria: three patients (9%). It is noteworthy that 77% of AEs were resolved within the first month [26].

**thalamotomiebedingte und gerätebezogene Komplikationen**

Thalamotomy-related complications were reported as contralateral weakness in three patients (8%), dysgeusia in one patient (3%), and gait instability in one patient (3%). On the other hand, MRI/ultrasound-related AEs such as dizziness 22%, scalp burning 16%, and nausea 8% were reported most often [27].

### Serious adverse events

**keine Evidenz**

No evidence was found to answer the research question [35, 36].

**2 nicht-vergleichende Studien: keine aufgetreten**

SAEs were reported in both non-comparative studies but did not occur [26, 27].

# 5 Certainty of evidence

**RCT: moderates bis hohes Verzerrungsrisiko**

The RCT's RoB [15] was assessed by the Cochrane Collaboration tool version 2 [20] to have some concerns for the 3-month FU due to bias in the measurement of outcomes. Whereas the long-term FU results show high RoB as nearly all patients within the CG crossed over to the IG. Furthermore, long-term non-comparative FU results are affected by substantial bias due to missing data.

**geringes bis entscheidendes Verzerrungsrisiko**

In the two comparative cohort studies [35, 36], the RoB was assessed by the ROBINS-I tool [37, 38]. Critical limitations were given due to confounding, selection bias, and missing data. Serious limitations were given due to bias in measuring intervention and outcomes. In the two observational studies [26, 27], RoB was moderate using the IHE checklist [21]. The overall RoB of the included studies was low to moderate as additional interventions (co-interventions) were not clearly described (see Appendix Table A-4, Table A-5, and Table A-6).

**Effektivität: sehr niedrige bis moderate Qualität der Evidenz**

The overall strength of evidence for the *efficacy* of tcMRgFUS using InSightec's Exablate 4000 compared to *sham* was moderate (tremor severity). On the other hand, comparing tcMRgFUS to *DBS or RF thalamotomy*, the overall strength of evidence was very low (tremor severity).

**Sicherheit: sehr niedrige bis moderate Qualität der Evidenz**

The overall strength of evidence for *safety* was very low (AEs and SAEs) to moderate (AEs and SAEs) comparing tcMRgFUS vs *sham* and very low (AEs and SAEs) comparing tcMRgFUS vs *DBS or RF thalamotomy*.

**Qualität der Evidenz nach GRADE**

GRADE uses four categories to rank the strength of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

The ranking according to the GRADE scheme for the research question can be found in the summary of findings table below (Table 5-1 and Table 5-2) and the evidence profiles in Appendix Table A-7 and Table A-8.

*Table 5-1:* ***TcMRgFUS vs sham procedure:*** *Summary of findings table of the transcranial magnetic resonance-guided high-intensity focused ultrasound treatment*

| Outcome | Effects | N of participants (studies) | Certainty | Comments |
|---|---|---|---|---|
| **Efficacy (measured at 3m)** | | | | |
| **Tremor severity (CRST)** | reduction by 47% vs 0.1%; from 18.1±4.8 to 9.6±5.1 vs from 16.0±4.4 to 15.8±4.9; **p<0.001** | 56 vs 20 (1 RCT) | Moderate ⊕⊕⊕◯ | Higher scores indicate more severe tremor |
| **Safety (3-12m)** | | | | |
| **Adverse events** | ***Comparative (at 3m):*** *e.g.*[44] *paresthesia/numbness 14 vs 1 (25 vs 5%), gait disturbance 9 vs 1 (16 vs 5%), limb dysmetria 5 vs 0 (9 vs 0%);* ***Non-comparative:*** *e.g. paresthesias/numbness 21 (38%), gait disturbance 20 (36%), head discomfort 17 (30%)* | 56 vs 20 (1 RCT) | Moderate ⊕⊕⊕◯ | |
| | *E.g. gait disturbance 8 (22.9%), numbness/tingling 6 (17.1%), hemiparesis 5 (14.3%);* ***MRI/ultrasound-related:*** *e.g. dizziness (21.5% ), scalp burning (16.4%), nausea (8.4%);* ***Thalamotomy-related:*** *e.g. contralateral weakness (7.5%)* | 35-40 (2 PCSs) | ⊕◯◯◯ Very low | |
| **Serious adverse events** | ***Non-comparative data:*** *dense and permanent hypesthesia of the dominant thumb and index finger: 1 (1.7%)* | 56 vs 20 (1 RCT) | Moderate ⊕⊕⊕◯ | |
| | 0 (0); 0 (0) | 35-40 (2 PCSs) | ⊕◯◯◯ Very low | |

*Abbreviations: m – months. N – number of patients. PCSs – prospective cohort studies. RCT – randomised controlled trial. tcMRgFUS – transcranial magnetic resonance-guided high-intensity focused ultrasound. vs – versus.*

[44] The three most often occurring events are reported for all studies.

*Table 5-2:* ***TcMRgFUS vs deep brain stimulation or radiofrequency thalamotomy:***
*Summary of findings table of the transcranial magnetic resonance-guided high-intensity focused ultrasound treatment*

| Outcome | Effects | N of participants (studies) | Certainty | Comments |
|---|---|---|---|---|
| **Efficacy (measured at 1-13m)** | | | | |
| **Tremor severity (CRST and self-defined[45] scale)** | **Pre:** 54.9 vs 59.5 vs 64.4; **Post:** 17.7 (55.7) vs 15.8 (62.8) vs 13.2 (79.5);<br>All 3 groups: **s.s.** from baseline; IG vs CGb: **s.s.**<br>**1m:** 21 (91.3) vs 17 (89.5) vs 17 (100); **12m:** 18 (78.3) vs 16 (84.2) vs 12 (70.6); n.s.[46] | 38 vs 106<br>(2 comparative cohort studies) | ⨁◯◯◯<br>Very low | Higher scores indicate more severe tremor |
| **Safety (measured at 1-13m)** | | | | |
| **Adverse events** | *3m: In tcMRgFUS less* ***haemorrhage.*** *In tcMRgFUS patients more* ***physical*** *events, resolved at the 12-month FU.*<br>*12m: In tcMRgFUS less* ***neurologic*** *and* ***hardware-related*** *events than DBS, except for paresthesia.*<br>**1m:** 3 (13.0) vs 1 (5.3) vs 10 (58.8); **12m:** 1 (4.4) vs 4 (21.1) vs 2 (11.8) | 38 vs 106<br>(2 comparative cohort studies) | ⨁◯◯◯<br>Very low | |
| | *E.g.*[47] *gait disturbance 8 (22.9%), numbness/tingling 6 (17.1%), hemiparesis 5 (14.3%);*<br>***MRI/ultrasound-related:*** *e.g. dizziness (21.5% ), scalp burning (16.4%), nausea (8.4%);*<br>***Thalamotomy-related:*** *e.g. contralateral weakness (7.5%)* | 75 (2 PCSs) | ⨁◯◯◯<br>Very low | |
| **Serious adverse events** | 0 (0);<br>0 (0) | 75 (2 PCSs) | ⨁◯◯◯<br>Very low | |

*Abbreviations: m – months. N – number of patients. PCSs – prospective cohort studies. tcMRgFUS – transcranial magnetic resonance-guided high-intensity focused ultrasound. vs – versus.*

[45] "Patient response (symptomatic efficacy) was categorized according to a disease-specific rating scale." Absent: complete tremor remission after surgery; Occasional: tremor persisted in a milder form (greater than 90% abolition); Partial: some improvement (greater than 50% abolition); No improvement: no improvement (less than 50% abolition); "Ratings of "absence" or "occasional" indicated successful treatment."

[46] Between-group differences at 1 month and 12 months.

[47] The three most often occurring events are reported for all studies.

# 6 Discussion

This systematic review aimed to compare unilateral transcranial MR-guided focused ultrasound system (tcMRgFUS) to sham, deep brain stimulation (DBS), and radiofrequency (RF) thalamotomy in terms of efficacy and safety outcomes. The claimed benefit of tcMRgFUS is being a non-invasive, incisionless thermal ablation technique for treating patients with essential tremor (ET). Therefore, tcMRgFUS avoids the need for open brain surgery. It further combines high-intensity focused ultrasound with real-time MRI.

**Ziel: tcMRgFUS vs. Scheinbehandlung, Tiefe Hirnstimulation oder Radiofrequenz-Thalamotomie**

## Summary of evidence

This systematic review identified the best available evidence consisting of one double-blinded, multicentre RCT (incl. post-hoc long-term FU) [15]; two retrospective comparative cohort studies [35, 36] and two prospective, non-comparative studies [26, 27]. The RCT [15] provides comparative data only at the 3-month FU.

**beste verfügbare Evidenz: 5 Studien inkl. 1 RCT**

In total, 320 patients were enrolled, with a mean age range from 63 to 72 years. InSightec's Exablate 4000 was used for treating patients with drug-resistant ET. Loss to FU occurred in two [27, 35] of five studies.

**320 Pts. zwischen 63 und 72 J.**

## Summary of clinical efficacy and safety

### TcMRgFUS vs sham procedure (population A)

#### *Efficacy*

Evidence was found indicating that tcMRgFUS compared to sham procedure may be more effective regarding tremor severity ($p<0.001$) assessed three months post treatment. The between-group difference could show a reduction of tremor severity by 47% (from 18.1±4.8 to 9.6±5.1) in the IG vs 0.1% (from 16.0±4.4 to 15.8±4.9) in the sham group. The CRST's total score was reduced by 41% (from 50.1±14.0 to 29.6±13) in the IG compared to 2% (from 44.1±12.7.0 to 43.1±13.1) in the CG. Furthermore, functional disability ($p<0.001$; 62% reduction) and HRQoL ($p<0.001$; 46% reduction) improved at the 3-month FU. No evidence could be found concerning the global assessment of the disease symptoms and length of hospital stay [15].

**s.s. Verbesserung v. Tremor, funktionelle Beeinträchtigung und LQ nach 3 Monaten**

#### *Safety*

At the 3-month FU period, numerous AEs occurred in the IG and CG of the RCT. Most often[48], paresthesias or numbness (25% vs 5%), gait disturbance (16% vs 5%), limb dysmetria (9% vs 0%), and disequilibrium sensation (5% vs 0%) were reported. However, no statistically significant differences between the two groups were reported in the RCT [15].

**RCT: unerwünschte Ereignisse z. B. Taubheitsgefühl, Gangstörungen**

Similarly, frequently occurring AEs in non-comparative studies were gait disturbance (2.9%), numbness/tingling (17.1%), hemiparesis (14.3%), and unsteady gait (14.3%). 77.3% of these AEs were resolved within the first month [26]. As *MRI/ultrasound-related AEs* most often occurred dizziness (21.5%), scalp burning (16.4%) and nausea (8.4%). Whereas contralateral weakness (7.5%) occurred most frequently as *thalamotomy-related AEs* [27].

**ähnliche Ergebnisse in 2 nicht-vergleichenden Studien**

[48] i.e. the four most-frequently adverse events

**1 schwerwiegendes unerwünschtes Ereignis**

One SAE (1.7%) occurred in the IG as opposed to none in the CG within the 12-month assessment [15]. No SAEs occurred in the non-comparative studies [26, 27].

#### TcMRgFUS vs deep brain stimulation or radiofrequency thalamotomy (population B)

##### *Efficacy*

**2 vergleichende Studien: uneindeutig in Tremor, keine s.s. Verbesserung der funktionellen Beeinträchtigung und LQ**

Comparing tcMRgFUS to DBS or RF thalamotomy, evidence was inconclusive: Tremor severity statistically significantly improved in one study (p-value not reported) [35] but not in the other study [36] assessed after 12 months post treatment. Functional disability and HRQoL did not statistically improve compared to DBS [35]. However, the other comparative study did not report on that [36]. Furthermore, no evidence could be found concerning the global assessment of the disease symptoms and length of hospital stay.

##### *Safety*

**2 vergleichende Studien: neurologische, physische und hardwarebedingte Ereignisse sowie Blutungen**

The reported AEs included a variety of neurologic, physical and hardware-related events as well as haemorrhage. TcMRgFUS patients generally had less neurologic and hardware-related events than DBS, except for paresthesia. At the 3-month FU period, there were also less haemorrhage events in the tcMRgFUS group. TcMRgFUS patients had tendentially more physical events at the 3-month FU, however, these events were resolved at the 12-month FU [35]. Less treatment-related complications occurred in the tcMRgFUS group compared to the RF thalamotomy or DBS groups [36].

**ähnliche Ergebnisse in 2 nicht-vergleichenden Studien**

The safety data are reported together as the studies reported on population A and B. Similarly, frequently occurring AEs in non-comparative studies were gait disturbance (2.9%), numbness/tingling (17.1%), hemiparesis (14.3%), and unsteady gait (14.3%). Notably, 77.3% of these AEs were resolved within the first month [26]. As *MRI/ultrasound-related AEs*, most often occurred dizziness (21.5%), scalp burning (16.4%) and nausea (8.4%)), and as *thalamotomy-related AEs,* contralateral weakness (7.5%) occurred most frequently [27].

**keine schwerwiegenden unerwünschten Ereignisse**

No SAEs occurred in the non-comparative studies [26, 27] and were not reported in the comparative cohort studies [35, 36].

### Internal and external validity

#### TcMRgFUS vs sham procedure (population A)

**sehr niedrige bis moderate Qualität der Evidenz**

Overall, the strength of evidence for the critical clinical *efficacy* outcome was moderate (tremor severity) due to the high RoB (RCT [15]). Regarding the *safety* outcomes of tcMRgFUS, the quality of evidence was very low (non-comparative studies [26, 27]) to moderate (RCT [15]) in both outcomes (i.e. AEs and SAEs). Evidence was downgraded due to the high RoB.

**moderates Verzerrungsrisiko**

Across the three included studies, RoB had some concerns at the 3-month FU (RCT [15]) and low RoB (non-comparative studies [26, 27]). Several limitations of the best available evidence need to be considered: Some concerns arose due to bias in the measurement of the outcome at the 3-month FU [15] and moderate RoB as additional interventions were not clearly described [27].

**kleine Studienpopulation**

The small number of enrolled participants across the studies (35-81 patients) could have influenced the occurrence of safety events. However, this can be explained by the rarity of the disease.

### TcMRgFUS vs deep brain stimulation or radiofrequency thalamotomy (population B)

**sehr niedrige bis moderate Qualität der Evidenz**

The strength of evidence for the critical clinical *efficacy* outcome was very low (tremor severity), mainly due to high RoB and imprecision (comparative cohort studies [35, 36]). Regarding *safety* outcomes, the quality of evidence was very low in both outcomes (i.e. AEs and SAEs) in all four included studies (comparative cohort studies [35, 36] and non-comparative studies [26, 27]). Evidence was downgraded due to the high RoB.

**geringes bis entscheidendes Verzerrungsrisiko**

Across the four included studies, RoB was critical in both comparative cohort studies [35, 36] but low RoB in the non-comparative trials [26, 27]. Several limitations of the best available evidence need to be considered: Critical RoB arose mainly due to confounding and selection bias of participants in the study [36] and bias due to missing data [35]; moderate RoB as additional interventions were not clearly described [27].

**kleine Studienpopulation**

The small number of enrolled participants across the studies (35-85 patients) could have influenced the occurrence of safety events. However, this can be explained by the rarity of the disease.

## Embedding into existing literature and interpretation of findings

**2 Meta-Analysen (395-617 Pts.) mit ähnlichen Ergebnissen**

Our findings align with recently published systematic reviews and meta-analyses [39, 40]. Analysing the efficacy and safety profile of tcMRgFUS for ET, 29 studies were found evaluating 617 patients [39]. A significant difference was observed comparing tremor severity, hand tremor, and functional disability before and after 12 months of tcMRgFUS. The most frequently observed procedure-complications were head pain and dizziness. Therefore, tcMRgFUS seems to be an effective procedure for relieving unilateral tremor in ET patients. At the FU assessments, the analysis revealed a decreasing trend in other complications [39]. A meta-analysis published in 2022 included 21 articles reporting on 395 patients. Tremor severity, hand tremor, and QoL statistically significantly improved after three months post treatment. Hand tremor significantly improved from baseline to the 24-month FU period. The treatment effect was slightly decreased at 36 months. The authors report a current paucity of long-term FUs in the literature [40].

**weitere systematische Übersichtsarbeiten von:**

**Health Quality Ontario**

**National Institute for Health and Care Excellence**

Currently, several recommendations of systematic reviews are given regarding tcMRgFUS in patients with drug-resistant ET with similar findings to ours. In 2018, '*Health Quality Ontario*' concluded that the given evidence shows that tcMRgFUS is generally effective and safe at reducing tremor severity, improving QoL and helping people get back to their daily activities. TcMRgFUS provides a treatment option for patients ineligible for invasive neurosurgery and offers a non-invasive option for all patients considering neurosurgery [41]. In the same year, *National Institute for Health and Care Excellence (NICE)* stated that no major safety concerns were found; however, the current evidence on efficacy is limited in terms of quantity. Therefore, tcMRgFUS should *not* be used unless there are special arrangements for clinical governance, consent, and audit or research [18].

**National Health Service**

**Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen**

**Medical Services Advisory Committee**

In 2020, the *National Health Service (NHS)* recommended that tcMRgFUS should be available as a treatment option through routine commissioning for the treatment of drug-resistant ET in patients who are not eligible for DBS. Therefore, they concluded that there is enough evidence to make the treatment available at this time and to support a policy for the routine commissioning of tcMRgFUS [42]. The *Institute for Quality and Efficiency in Health Care* (IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen) summarised in their report published in 2021 a benefit of tcMRgFUS compared to conservative treatment alone for patients not or not yet eligible for DBS. For patients eligible for DBS, neither superiority nor inferiority compared to DBS could be identified [16]. In 2022, the Australian '*Medical Services Advisory Committee'* stated in their report that tcMRgFUS has non-inferior efficacy compared to DBS, although limitations in the clinical evidence were noted. Therefore, they supported the creation of new Medicare Benefits Schedule items for tcMRgFUS to treat drug-resistant ET [43].

**Limitationen des RCT: keine Vergleichsdaten bei Langzeitbeobachtung, nur wenige Pts. und könnten Gruppenzugehörigkeit vermutet haben was die Ergebnisse beeinflusst haben könnte**

For patients who are not eligible or yet not eligible for DBS, the best available evidence found for the present review was a double-blinded, multicentre RCT [15]. However, limitations and critiques on this RCT are given. Even if FU studies up to five years are published, comparative data are only available at the 3-month FU, which limits the evidence [44]. The majority of side effects occurred on the day after tcMRgFUS. Therefore, these patients could have correctly deduced that they had undergone tcMRgFUS rather than the sham procedure. As criticised by other authors [45], this might have affected patients' expectations for disease improvement. Furthermore, as 76 patients were recruited in eight centres in total, only a small number of patients were treated at each centre, which may have affected the RCT's findings [45].

**tcMRgFUS wird auch bei Morbus Parkinson angewendet**

**sicher und Verbesserung v. Tremor und LQ**

This report focused on assessing tcMRgFUS in *ET* patients. This intervention can also be used for Parkinson's disease patients and was assessed for efficacy and safety at 12-month FU. 27 Parkinson's patients were randomised (2:1) to tcMRgFUS or sham procedure. Also, for Parkinson's disease, drug-resistant tremor improved, even in this setting of a placebo response [46]. A systematic review confirmed this finding, including eleven studies assessing 80 patients. A decline in tremor severity and improvement of QoL was observed after tcMRgFUS. The treatment did not significantly affect neuropsychological outcomes, and most AEs were transient and mild [47]. Also, in studies with mixed populations (i.e. Parkinson's and ET patients), effective and safe characteristics of tcMRgFUS were stated [48, 49].

**Faktoren für Wiederauftreten von Tremor z. B. ungenaue Thalamotomie, Größe der Läsion**

Relapse of tremor is a crucial topic. A case-control study identified possible relevant factors contributing to tremor relapse after tcMRgFUS in patients with ET and Parkinson's disease. They found that the most relevant determining factors for tremor relapse appear to be inaccurate thalamic targeting and tremor from Parkinson's disease. Furthermore, the size of the thalamotomy lesion can influence the outcome of tcMRgFUS [50].

**andere interessante Endpunkte:**

**psychiatrische Störungen, Komorbiditäten, Gesundheitsressourcen, Kosten ...**

In the current report, tremor severity, functional disability, and HRQoL outcomes were synthesised. These outcomes were most often found in literature, although other interesting outcomes such as cognitive safety, neurological AEs or comorbidities are investigated. A large retrospective observational study including 5,286 patients assessed psychiatric disorders, comorbidities, healthcare resource utilisation, and costs among ET patients compared with patients without ET in real-world settings. The authors reported that 26% of patients had no insurance claims for ET-related invasive therapies or pharmacotherapy 12 months following the index date. ET patients had more

comorbidities than non-ET patients, a higher prevalence of psychiatric disorders, and thus higher total healthcare costs. Therefore, increased comorbidity, mental health, and healthcare cost burdens among patients with ET compared with matched patients without ET could be demonstrated [51].

**... kognitive Sicherheit, Häufigkeit/Schwere von (neurologischen) unerwünschten Ereignissen**

Cognitive safety after unilateral tcMRgFUS for ET was evaluated at a 12-month FU period, and satisfactory response in terms of tremor benefit and no sign of cognitive worsening after the procedure were shown. TcMRgFUS does not carry a clinically meaningful risk of cognitive impairment. However, the total number of patients studied so far remained relatively small, and the important attrition rate could have biased the sample to reach a definitive conclusion [52]. Furthermore, the safety profile was assessed, including frequency and severity of (S)AEs and neurological AEs. The study supported the overall safety profile of tcMRgFUS for patients with drug-resistant ET [53].

## Limitations

**Beobachtungsstudien für Sicherheitsendpunkte eingeschlossen**

The main limitation of the report is that, for safety, we included observational studies (if >20 patients enrolled) in our analysis. Some methodologists may consider it to be a weakness to have included observational studies next to randomised trials within the evidence synthesis. To mitigate concerns, we have carefully selected these studies based on design features (excluding retrospective single-arm studies) and the number of patients (small case series ≤20 enrolled patients). This aligns with the Cochrane methodology, and we believe we better understood safety by including observational studies in our report [54].

**keine „linked evidence" eingeschlossen, andere interessante Endpunkte nicht untersucht**

We did not include linked evidence. While this evidence may be useful in theory, the possibility that the evidence would have changed is low as the IQWiG report [16] included linked evidence and did not derive at a diverging evidence synthesis. Furthermore, this report did not assess other interesting outcomes, such as cognitive safety, neurological AEs, psychiatric disorders, comorbidities, healthcare resource utilisation, and costs. However, these outcomes were out of the scope.

**nur 1 RCT und 2 retrospektive Vergleichsstudien**

The main limitation of the evidence is that only one RCT (tcMRgFUS vs sham) and two retrospective comparative cohort studies (tcMRgFUS vs DBS or RF thalamotomy) could be identified, investigating drug-resistant ET.

## Evidence gaps, applicability and ongoing studies

**Wissenslücken z. B. vergleichende Langzeitergebnisse**

Evidence gaps concerning tcMRgFUS vs sham (population A), such as the lack of comparative long-term data, could be observed. In addition, more evidence of well-designed head-to-head RCTs comparing tcMRgFUS to other therapies is needed. Future research should focus on more high-quality RCTs with comprehensive safety reporting and long-term FUs, including larger cohorts of subjects.

**bilaterale tcMRgFUS: einzelne Studien mit positiven Ergebnissen, jedoch mehr Forschungsbedarf notwendig**

In our review, all included studies performed unilateral tcMRgFUS, as recommended by the AWMF, but not bilateral tcMRgFUS [13]. There is still little evidence regarding bilateral tcMRgFUS. In a case series, the authors found that bilateral tcMRgFUS for ET is feasible and might be effective and safe for head and voice tremor [55]. A single-arm study determined that staged bilateral tcMRgFUS can be performed with a reasonable safety profile, similar to unilateral thalamotomy. It improved tremor and QoL of patients with ET. However, long-term FUs are required to validate these findings [56].

**verschiedene Komparatoren, Messinstrumente, Beobachtungszeiträume, Länder und primäre vs. sekundäre Endpunkte**

In the current review, different comparators (i.e. sham, DBS, RF thalamotomy) were used and might have hindered the applicability of the study's results. Tremor severity was reported in all included studies except in one of the prospective non-comparative studies [4]. This outcome was reported as the primary outcome measure in only two of the five included studies [2, 5], whereas the other three studies [1, 3, 4] did not state any primary endpoints, which may minimise the study results' applicability, especially since their power is not calculated. In one study [36], the tremor severity was assessed based on a self-defined scale. Furthermore, the FU duration considerably differs among the included publications (1 to 60 months). The included studies were conducted in different geographical regions (e.g. Japanese population with a lower skull density ratio than the US[49]), which may limit the applicability of the results (see Table A-9). All these limitations and evidence gaps should be considered for future studies.

**laufende Studie schließt ev. Wissenslücke hinsichtlich Langzeitergebnissen**

The search for ongoing studies revealed that there is currently one ongoing RCTs (JPRN-UMIN000010714) sponsored by InSightec. It compares the efficacy and safety of tcMRgFUS to sham procedure within a 12-month FU in patients with drug-resistant ET. The planned numbers of subjects to be included in the trial are ten patients, and the measured primary outcome is tremor severity. The estimated completion date is not reported (see Table A-10). As proposed, this ongoing study will not cover all evidence gaps mentioned above.

## Conclusion

**tcMRgFUS ist hinsichtlich der Scheinbehandlung überlegen**

The evidence indicates that tcMRgFUS is superior to sham procedure in terms of tremor severity, functional disability, and HRQoL at the 3-month FU period in patients with drug-resistant ET who are not eligible or not yet eligible for DBS (population A). Safety data indicate that tcMRgFUS may be a safe treatment option for this patient population.

**Pts. bei welchen Tiefe Hirnstimulation möglich: Evidenzlage unzureichend**

For patients eligible for DBS (population B), the evidence is insufficient to assess comparative efficacy and safety of tcMRgFUS due to the retrospective design of the studies. Randomised, well-conducted, comparative studies are needed, focusing on directive comparing tcMRgFUS in patients eligible for DBS and long-term safety in large registry-based studies.

[49] In Japan, the application of unilateral tcMRgFUS to treat ET and Parkinson's disease has been covered by health insurance since 2019 and 2020, respectively [57].

# 7 Recommendation

In Table 7-1, the scheme for recommendations is displayed, and the according choice is highlighted.

*Table 7-1: Evidence-based recommendations*

| | |
|---|---|
| | The **inclusion** in the catalogue of benefits is **recommended**. |
| **X** | The **inclusion** in the catalogue of benefits is **recommended with restrictions**. |
| | The inclusion in the catalogue of benefits is **currently not recommended**. |
| | The **inclusion in** the catalogue of benefits is **not recommended**. |

Reasoning:

**Population A: tcMRgFUS sicher und effektiver als Scheinbehandlung**

For patients who are not eligible or not yet eligible for DBS (population A), the current evidence indicates that the assessed technology tcMRgFUS is safe and more effective in terms of tremor severity, functional disability, and HRQoL in patients with drug-resistant ET than the comparator of sham procedure. However, comparative long-term evidence is needed. For patients eligible for DBS (population B), the evidence is insufficient to assess comparative efficacy and safety of tcMRgFUS due to the retrospective design of the studies.

**Empfehlung zugunsten restriktiver Erstattung**

TcMRgFUS should thereby be restricted to selected patients and limited to specialised clinical settings. New study results will potentially influence the effect estimate considerably. An RCT (n=10) with a 12-month FU and patient-relevant primary outcomes is ongoing (JPRN-UMIN000010714); however, the date of completion is not reported.

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# Appendix

## Evidence tables of individual studies included for clinical efficacy and safety

*Table A-1: Transcranial magnetic resonance-guided high-intensity focused ultrasound: results from randomised controlled studies and four single-arm follow-up studies*

| Name, year | Elias 2016[50] (primary analysis with 1y FU) [15], Chang 2018 (2y FU) [31], Halpern 2019 (3y FU) [32], Park 2019 (4y FU) [33], Cosgrove 2022 (5y FU) [34] |
|---|---|
| **Study characteristics** | |
| **Country** | United States, Canada, Japan, South Korea |
| **Sponsor(s)** | InSightec, Focused Ultrasound Foundation, Binational Industrial Research and Development (BIRD) Foundation |
| **Intervention/Product** | Focused ultrasound thalamotomy (unilateral) |
| **Comparator** | Sham procedure[51] |
| **Study design** | Double-blinded, multicentre RCT (incl. post-hoc long-term FU) |
| **Study duration[52]** | NR |
| **Number of enrolled pts** | 81 |
| **Number of analysed pts** | 76 randomised/analysed into a 3:1 ratio<br>IG 56 vs CG 20 |
| **Number of pts with ET** | 100% |
| **Loss to follow-up (n (%))** | 0 (0) until group comparison at 3m |
| **Crossover** | 3 (incomplete procedure) vs 19 (after 3m blinded period) |
| **Indication** | Pts with drug-resistant ET |
| **Inclusion criteria** | ■ Postural or intention tremor of the hand that was moderate to severe[53] and disabling[54] tremor<br>■ Drug-resistant tremor to at least 2 trials of medical therapy, including at least 1 first-line agent (propranolol or primidone)<br>■ Stable medication dose of concurrent medical therapy for 30 days before randomisation |
| **Follow-up (months post treatment)** | Primary analysis: 3m, 6m, 12m [15]<br>FUs: 24m (2y) [31], 36m (3y) [32], 48m (4y) [33], 60m (5y) [34] |

[50] In the study protocol, a crossover RCT was planned. In the NEJM publication, it is reported as a 'normal' RCT.

[51] After 3 months, patients in the sham procedure group could cross over to active treatment.

[52] Time period when treatments occurred.

[53] Defined by a score of ≥2 on the CRST

[54] Defined by a score of ≥2 on any of the eight items in the disability subsection of the CRST

| Name, year | Elias 2016[50] (primary analysis with 1y FU) [15], Chang 2018 (2y FU) [31], Halpern 2019 (3y FU) [32], Park 2019 (4y FU) [33], Cosgrove 2022 (5y FU) [34] | |
|---|---|---|
| **Patient characteristics** | | |
| **Age of pts (yrs; mean (SD))** | 71.0±8.3 (n=76)<br>IG 70.8±8.7 vs CG 71.4±7.3 | |
| **Gender (male, %)** | 68% male | |
| **Disease duration (yrs; mean±SD)** | 16.8±12.3 (n=76)<br>From initial symptoms: IG 28.3±16.4 vs CG 27.9±14.9<br>From initial diagnosis: IG 16.4±13.1 vs CG 17.8±10.2<br>From start of medical therapy: IG 13.9±10.7 vs CG 14.7±10.5 | |
| **Right-handed (%)** | 83% | |
| **Comorbidities** | NR | |
| **Outcomes** | | |
| **Efficacy** | | |
| **Outcome measurements** | **CRST, QUEST** | **CRST, QUEST** |
| | **Comparative data (measured at 3m; IG vs CG)** | **Non-comparative data** |
| **Tremor (number of pts; mean±SD; p-value; 95%CI)** | **Hand tremor (CRST part A and B):**<br>**Mean CRST change score (between-group difference):**<br>■ ***3m (n=76):*** red. by 47% (from 18.1±4.8 to 9.6±5.1) vs 0.1% (from 16.0±4.4 to 15.8±4.9) **p<0.001**<br>■ 8.3 points, 95%CI, 5.9 to 10.7<br>**Mean CRST change score (total score):**<br>■ ***3m (n=76):*** red. by 41% (from 50.1±14.0 to 29.6±13) vs 2% (from 44.1±12.7.0 to 43.1±13.1) | **Hand tremor (CRST part A and B):**<br>**Mean CRST change score:**<br>■ ***12m (n=70):*** from 18.1±4.8 at baseline to 10.9±4.5; **p<0.001** → 40% red.<br>■ 7.2 points, 95% CI, 6.1 to 8.3<br>■ ***24m (n=67[55]):*** from 19.8±4.9 at baseline to 8.8±5.0; **p<0.001** → red. by 56%<br>11 points, 95%CI, 7.6 to 10.0<br>■ ***36m (n=52):*** from 20.1±4.7 at baseline to 9.5±5.4; **s.s.** → red. by 56%<br>■ ***48m (n=12[55]):*** from 17.4±3.8 at baseline to 7.7±4.1 4; **p=0.013** → red. by 56%<br>■ ***60m (n=40):*** from 3±0.97 at baseline to 0.8±1.0; **p<0.0001** → red. by 73.1%<br>**Mean CRST change score (total score):**<br>■ ***12m (n=70):*** red. by 35% (from 50.1±14.0 to 32.4±14.5)<br>■ ***24m:*** NR<br>■ ***36m:*** NR<br>■ ***48m:*** NR<br>■ ***60m:*** NR |

[55] In Cosgrove 2022 [34] it is stated that ", 70 patients were observed at 12 months, 50 at 2 years, 52 at 3 years, 45 at 4 years, and 40 at 5 years." However, Chang 2018 [31] reported on 67 patients.

| Name, year | Elias 2016[50] (primary analysis with 1y FU) [15], Chang 2018 (2y FU) [31], Halpern 2019 (3y FU) [32], Park 2019 (4y FU) [33], Cosgrove 2022 (5y FU) [34] | |
|---|---|---|
| **Functional disability (number of pts; mean±SD; p-value; 95%CI)** | **Disability (CRST part C):**<br>■ ***3m (n=76):*** 62% red. (from 16.5±4.6 to 6.2±5.6) vs 3% red. (from 16.0±4.3 to 15.6±4.6); **p<0.001** | **Disability (CRST part C):**<br>■ ***12m (n=70):*** red. from 16.5±4.6 to 6.3±6.2<br>■ ***24m (n=67):*** from 16.4±4.5 at baseline to 6.5±5.0; **p<0.001** → red. by 60%<br>■ 9.9 points; 95%CI, 5.3-7.7<br>■ ***36m (n=52):*** from 16.4±4.6 at baseline to 7.5±6.1; **s.s.** → red. by 63%<br>■ ***48m (n=12):*** from 12.7±3.0 at baseline to 4.7±3.0; P=0.007 → red. by 63%<br>■ ***60m (n=40):*** from 16±4.6 at baseline to 8.9±6.6; **p<0.0001** → red. by 44.5% |
| **Health-related quality of life (number of pts; mean±SD; p-value)** | **Quality of life (QUEST):**<br>■ ***3m (n=76):*** 46% red. (from 42.6±18.3 to 23.1±16.9) vs 3% red. (from 42.8±19.5 to 41.4±19.4); **p<0.001** | **Quality of life (QUEST):**<br>■ ***12m (n=70):*** NR<br>■ ***24m (n=67):*** NR<br>■ ***36m (n=52):*** from 43.1±18.3 at baseline to 23.8±19.6 → red. by 50%<br>■ ***48m (n=12):*** NR<br>■ ***60m (n=40):*** from 43± 18 at baseline to 30±20; **p<0.0003** |
| **Global assessment of the disease symptoms** | NR | |
| **Length of hospital stay** | NR | |
| **Safety (from [15])** | | |
| | **Comparative data (measured at 3m; IG vs CG)** | **Non-comparative data (total)** |
| **Adverse events (n (%))** | *Most often[56] were reported: paresthesias or numbness (14 (25%) vs 1 (5%)), gait disturbance (9 (16%) vs 1 (5%)), limb dysmetria (5 (9%) vs 0 (0%)), and disequilibrium sensation (3 (5%) vs 0 (0%)).*<br>***Paresthesias or numbness, any region:*** **14 (25) vs 1 (5)**<br>***Taste disturbance:*** **2 (4) vs 0 (0)**<br>***Gait disturbance, any, objective, or subjective:*** **9 (16) vs 1 (5)**<br>***Dysmetria, limb:*** **5 (9) vs 0 (0)**<br>***Weakness, contralateral:*** **2 (4) vs 0 (0)**<br>***Dysarthria:*** **1 (2) vs 0 (0)**<br>***Dysphagia:*** **1 (2) vs 0 (0)**<br>***Headache lasting >1 day:*** **2 (2) vs 4 (20)**<br>***Fatigue:*** **1 (2) vs 1 (5)**<br>***Disequilibrium sensation:*** **3 (5) vs 0 (0)**<br>***Tinnitus:*** **0 (0) vs 0 (0)** | ***Paresthesias or numbness, any region:*** 21 (38)<br>***Taste disturbance:*** 3 (5)<br>***Gait disturbance, any, objective, or subjective:*** 20 (36)<br>***Dysmetria, limb:*** 7 (12)<br>***Weakness, contralateral:*** 2 (4)<br>***Dysarthria:*** 1 (2)<br>***Dysphagia:*** 1 (2)<br>***Headache lasting >1 day:*** 8 (14)<br>***Fatigue:*** 3 (5)<br>***Disequilibrium sensation:*** 5 (9)<br>***Tinnitus:*** 3 (5) |

[56] i.e. the four most-frequently occurred events

| Name, year | Elias 2016[50] (primary analysis with 1y FU) [15], Chang 2018 (2y FU) [31], Halpern 2019 (3y FU) [32], Park 2019 (4y FU) [33], Cosgrove 2022 (5y FU) [34] | |
|---|---|---|
| **Adverse events (n (%))** *(continuation)* | ***Intraprocedural sensations or events:***<br>Head discomfort: "heat" or "pressure": **0 (0) vs 0 (0)**<br>Vertigo: "dizzy": **0 (0) vs 0 (0)**<br>Nausea: **0 (0) vs 2 (10)**<br>Vomiting: **0 (0) vs 0 (0)**<br>Scalp tingling: **0 (0) vs 1 (5)**<br>Back pain: **0 (0) vs 1 (5)**<br>Anxiety: **0 (0) vs 2 (10)**<br>***Pin-site pain, oedema, or bruising attributable to placement of the stereotactic frame:*** **0 (0) vs 7 (35)**<br>***No AEs:*** **0 (0) vs 8 (40)** | ***Intraprocedural sensations or events:***<br>Head discomfort: "heat" or "pressure": 17 (30)<br>Vertigo: "dizzy": 12 (21)<br>Nausea: 11 (20)<br>Vomiting: 2 (4)<br>Scalp tingling: 4 (7)<br>Back pain: 5 (9)<br>Anxiety: 3 (5)<br>***Pin-site pain, oedema, or bruising attributable to placement of the stereotactic frame:*** 17 (30)<br>***No AEs:*** 6 (11) |
| **Serious adverse events (n (%))** | NR | ***Dense and permanent hypesthesia of the dominant thumb and index finger:*** 1 (1.7) |

*Abbreviations: AEs – adverse events. BIRD – Binational Industrial Research and Development. CG – control group. CRST – Clinical Rating Scale for Tremor. ET – essential tremor. FU(s) – follow-up(s). IG – intervention group. m – months. n – number of patients. NR – not reported. pts – patients. QUEST – Quality of life in Essential Tremor Questionnaire. red. – reduction. SD – standard deviation. s.s – statistically significant. vs – versus. yrs – years.*

*Table A-2: Transcranial magnetic resonance-guided high-intensity focused ultrasound: results from comparative cohort studies*

| Author, year | Huss 2015 [35] | Kim 2017 [36] |
|---|---|---|
| **Study characteristics (IG vs CGu vs CGb [35] or IG vs CGDBS vs CGRF [36])** | | |
| **Country** | United States | South Korea |
| **Sponsor(s)** | None[57] | NR |
| **Intervention/Product** | Focused ultrasound thalamotomy (unilateral)<br>NeuroAblate 4000, InSightec, Israel | TcMRgFUS (unilateral)<br>ExAblate 4000 device, InSightec, Israel |
| **Comparator** | Bilateral or unilateral thalamic DBS | RF thalamotomy or DBS |
| **Study design** | Retrospective comparative cohort study | Retrospective comparative cohort study |
| **Study duration[52]** | January 2004 – July 2013 | 1995 – 2014[58] |
| **Number of enrolled pts** | 85<br>15 vs 13 vs 57 | 59<br>23 vs 19 vs 17 |
| **Number analysed pts** | 73<br>15 vs NR vs NR[59] | 59<br>23 vs 19 vs 17 |

[57] "FUS treatments were previously funded by the FUS Foundation, not specifically for this study."

[58] "Unilateral RF thalamotomy procedures were only performed until 2004." DBS and tcMRgFUS patients "who underwent treatment between 2012 and 2014 were included in the analysis."

[59] "Twelve patients, all of whom were treated with DBS, with missing information or incomplete evaluations were excluded from the analysis."

| Author, year | Huss 2015 [35] | Kim 2017 [36] |
|---|---|---|
| Number of pts with ET (%) | 100% | 100% |
| Loss to follow-up (n (%)) | 12 (14)[59] | 0 (0) |
| Indication | Drug-resistant severe ET | Drug-resistant ET |
| Inclusion criteria | ■ Drug-resistant ET<br>■ Preoperative and postoperative evaluation using the CRST and QUEST | ■ Drug-resistant ET<br>■ Minimum FU of 12m<br>Record of outcome assessments (efficacy, treatment-related complications) |
| Follow-up (months post treatment; months (mean) [35] or months (absolute) [36]) | 12[60] vs 13[61] | 1, 12 |
| **Patient characteristics (IG vs CGu vs CGb [35] or IG vs CGDBS vs CGRF [36])** | | |
| Age of pts (yrs; mean) | 67.2 vs 71.7 vs 63.5 | 64.7 vs 62.8 vs 64.5 |
| Gender (male, %) | 66.7 vs 61.5 vs 66.7 | 87.0 vs 68.4 vs 53.0 |
| Disease duration (yrs; mean) | NR | 20.5 vs 14.1 vs 20.8 |
| Handedness (right; %) | 80.0 vs 61.5 vs 85.9 | NR |
| Comorbidities | NR | NR |
| **Outcomes** | | |
| **Efficacy (IG vs CGu vs CGb [35] or IG vs CGDBS vs CGRF [36])** | | |
| **Outcome measures** | **CRST, QUEST** | **Self-defined scale62** |
| **Tremor (points (% from baseline) [35] or n (%) [36])** | **Tremor severity (CRST total score):**<br>***Pre:*** 54.9[63] **vs** 59.5 **vs** 64.4<br>***Post:*** 17.7 (55.7), s.s. from baseline **vs** 15.8 (62.8), **s.s.** from baseline **vs** 13.2 (79.5), **s.s.** from baseline<br>IG vs CGb: **s.s.** | **Tremor severity (changes in tremor severity; successful treatment[64]):**<br>***1m:*** 21 (91.3) vs 17 (89.5) vs 17 (100)<br>Between-group differences: n.s.<br>***12m:*** 18 (78.3) vs 16 (84.2) vs 12 (70.6)<br>Between-group differences: n.s |

[60] One patient hat only a 3-month follow-up.

[61] Unilateral *and* bilateral DBS surgeries

[62] "Patient response (symptomatic efficacy) was categorized according to a disease-specific rating scale." Absent: complete tremor remission after surgery; Occasional: tremor persisted in a milder form (greater than 90% abolition); Partial: some improvement (greater than 50% abolition); No improvement: no improvement (less than 50% abolition); "Ratings of "absence" or "occasional" indicated successful treatment."

[63] „Denotes statistically significant difference from bilateral DBS ($P<0.05$)."

[64] Defined as "absence of or occasional symptoms"

| Author, year | Huss 2015 [35] | Kim 2017 [36] |
|---|---|---|
| **Tremor (points (% from baseline) [35] or n (%) [36])** *(continuation)* | **Observed tremor (CRST part A[65]):**<br>***Pre:*** 13.4[63] **vs** 19.1 **vs** 22.1<br>***Post:*** 8.7 (35.1), **s.s.** from baseline **vs** 8.4 (56.0), **s.s.** from baseline **vs** 3.8 (82.8), **s.s.** from baseline<br>IG vs CGb: **s.s.** | |
| **Functional disability (points (% from baseline) [35])** | **Disability (CRST part C):**<br>***Pre:*** 18.2 **vs** 18.9 **vs** 19.9<br>***Post:*** 2.8 (85.4), s.s. from baseline **vs** 3.2 (83.1), s.s. from baseline **vs** 2.3 (88.4), s.s. from baseline<br>IG vs CGb: n.s. | NR |
| **Health-related quality of life (% [35])** | **Quality of life:**<br>***Pre:*** IG: 37.5[63]; CGb: 52.1<br>***Post:*** IG: 68.0, s.s. from baseline; CGb: 72.0, s.s. from baseline<br>IG vs CGb: n.s. | NR |
| **Global assessment of the disease symptoms** | NR | NR |
| **Length of hospital stay** | NR | NR |
| **Outcomes** | | |
| **Safety (IG vs CGu vs CGb [35] or IG vs CGDBS vs CGRF [36])** | | |
| **Adverse events (n [35] or n (%) [36])** | *AEs include a variety of neurologic, physical and hardware-related events as well as haemorrhage. At the 12-month FU, TcMRgFUS patients generally had less **neurologic** (e.g. dysarthria) and **hardware-related** (e.g. lead erosion) events than DBS, except for paresthesia where more cases occurred in the tcMRgFUS group. At the 3-month FU, there was also less **haemorrhage** in the tcMRgFUS group. TcMRgFUS patients had tendentially more **physical** events at the 3-month FU, resolved at the 12-month FU.* | *There occurred less **treatment-related** complications in the tcMRgFUS group compared to the RF thalamotomy or DBS groups.*<br>**Treatment-related complications:**<br>■ ***1m:*** 3 (13.0)[66] vs 1 (5.3)[67] vs 10 (58.8)[68]<br>■ ***12m:*** 1 (4.4)[69] vs 4 (21.1)[70] vs 2 (11.8)[71] |

[65] Part B was not assessed.

[66] Mild facial paresis (n=1), balance problems (n=1), not reported in the study (n=1)

[67] Mild facial paresis (n=1)

[68] During the first week after surgery (complications are counted multiple times): intracerebral hemorrhage near the lesion (n=2), cognitive deterioration (n=1), mild dysarthria (n=5), impaired eye movement (n=1), mild facial paresis (n=3), hypesthesia (n=1), loss of taste (n=1)

[69] Mild facial paresis (n=1)

[70] Balance problems (n=3), muscle twitching in the contralateral forearm (n=1)

[71] Mild dysarthria (n=1), mild facial paresis (n=1)

| Author, year | Huss 2015 [35] | Kim 2017 [36] |
|---|---|---|
| **Adverse events (n [35] or n (%) [36])** *(continuation)* | **Neurologic:**<br>■ **Paresthesia:** ***0-3m***[72]***:*** 14 vs 1 vs 2; ***12m:*** 3 vs 2 vs 1<br>■ **Dysarthria:** ***0-3m:*** 1 vs 1 vs 10; ***12m:*** 0 vs 0 vs 6<br>■ **Dysphagia:** ***0-3m:*** 0 vs 0 vs 2; ***12m:*** 0 vs 0 vs 0<br>■ **Gait instability:** ***0-3m:*** 5 vs 11 vs 10; ***12m:*** 0 vs 0 vs 0<br>■ **Weakness:** ***0-3m:*** 1 vs 1 vs 4; ***12m:*** 0 vs 0 vs 1<br>■ **Mental status change:** ***0-3m:*** 0 vs 1 vs 3; ***12m:*** 0 vs 0 vs 3<br>**Physical (brief intraprocedural symptoms):**<br>■ **Headache:** ***0-3m:*** 9 vs 0 vs 0; ***12m:*** 0 vs 0 vs 0<br>■ **Lightheaded/dizzy:** ***0-3m:*** 11 vs 0 vs 0; ***12m:*** 0 vs 0 vs 0<br>■ **Nausea/vomiting:** ***0-3m:*** 8 vs 0 vs 0; ***12m:*** 0 vs 0 vs 0<br>■ **Flushed warmth:** ***0-3m:*** 4 vs 0 vs 0; ***12m:*** 0 vs 0 vs 0<br>**Hardware related:**<br>■ **Infection:** ***0-3m:*** 0 vs 0 vs 0; ***12m:*** 0 vs 0 vs 1<br>■ **Lead erosion:** ***0-3m:*** 0 vs 0 vs 1; ***12m:*** 0 vs 0 vs 2<br>■ **MRI burn at frame pin site:** ***0-3m:*** 2 vs 0 vs 0; ***12m:*** 0 vs 0 vs 0<br>**Haemorrhage:** ***0-3m:*** 0 vs 0 vs 2; ***12m:*** 0 vs 0 vs 0 | |
| **Serious adverse events (n (%))** | NR | NR |

*Abbreviations: tcMRgFUS – (transcranial) magnetic resonance-guided focused ultrasound surgery. CG – control group. CGb – control group (bilateral deep brain stimulation). CGDBS – control group (deep brain stimulation). CGRF – control group (radiofrequency). CGu – control group (unilateral deep brain stimulation). CRST – Clinical Rating Scale for Tremor. DBS – deep brain stimulation. FTM – Fahn-Tolosa-Marin. FU – follow-up. m – month(s). IG – intervention group. ET – essential tremor. NR – not reported. n.s. – not statistically significant (p>0.05). pts – patients. QUEST – Quality of life in Essential Tremor Questionnaire. RF – radiofrequency. s.s. – statistically significant (p<0.05). USA – United States of America.*

[72] Transient 0-3 months

*Table A-3: Transcranial magnetic resonance-guided high-intensity focused ultrasound: results from prospective non-comparative studies*

| Author, year | Abe 2021 [26] | Saporito 2022 [27] |
|---|---|---|
| **Study characteristics** | | |
| **Country** | Japan[73] | Italy |
| **Sponsor(s)** | Supported by InSightec (Haifa, Israel) | None |
| **Intervention/Product** | Focused ultrasound thalamotomy (unilateral)<br>ExAblate model 4000 (InSightec, Israel) | Focused ultrasound thalamotomy (unilateral)<br>ExAblate model 4000 (InSightec, Israel) |
| **Study design** | Prospective, multicentre single-arm confirmatory trial | Prospective, single-centre non-comparative study |
| **Study duration**[52] | March 2015 to March 2016 | NR |
| **Number of enrolled pts** | 35 | 60 |
| **Number analysed pts** | 35 | 40 |
| **Number of pts with ET (n (%))** | 100% | 22 (55)[74] |
| **Loss to follow-up (n (%))** | 0 (0) | 20 (33.3) |
| **Indication** | Disabling drug-resistant ET | Drug-resistant ET |
| **Inclusion criteria** | ■ ≥22y old<br>■ Diagnosis of moderate[75] to severe disabling[76] postural or intentional tremor in the dominant upper extremity by specialist neurologists<br>■ Tremor had to be drug-resistent<br>■ Doses were required to have been stable with no changes | ■ Age >18y<br>■ Signed informed consent to be enrolled in the study<br>Willingness to return for protocol-required FU visits |
| **Follow-up (months post treatment)** | 12 | 6 |
| **Patient characteristics** | | |
| **Age of pts (yrs; mean (SD))** | 71.3±9.3 | 69.5±10.0 |
| **Gender (male, %)** | 77 | NR |
| **Disease duration (yrs; mean (SD))**<br>■ **From initial symptoms**<br>■ **From initial diagnosis** | <br>■ 24.2±17.3<br>■ 9.2±8.2 | 13.10±10.02 |
| **Dominant hand (contralateral to the treated side; n (%))** | Right 34 (97.1%); Left 1 (2.9%) | NR |
| **Comorbidities** | NR | NR |

[73] "Previous trials have focused on populations with an SDR ≥0.45 ± 0.05, making the results unsuited for the Japanese population (≥0.30 ± 0.05)."

[74] Only data of patients with essential tremor were extracted.

[75] "Moderate tremor severity was defined as a ≥2 score on the postural or action item of the validated Clinical Rating Scale for Tremor (CRST; range=0-4 for any component)."

[76] "Significant disability was defined as a ≥2 score on any of the 8 daily activity items in the Disability subsection of the CRST."

| Author, year | Abe 2021 [26] | Saporito 2022 [27] |
|---|---|---|
| **Outcomes** | | |
| **Efficacy** | | |
| **Outcome measures** | **CRST, QUEST** | **FAB, QUEST** |
| **Tremor**<br>**(mean (95% CI); p-value)** | **Tremor/motor function score of the treated hand (CRST):**<br>■ ***Baseline***: 18.5 (95% CI: 16.7-20.3)<br>■ ***3 months***: 8.2 (95% CI: 6.1-10.3) → red. by 56.5% (95% CI: 45.1%-67.8%; **p<.001**)<br>■ ***6 months***: NR<br>■ ***12 months***: → red. by 56.4% (95% CI: 46.7%-66.1%; **p<.001**)<br>**Tremor/motor function score for the non-treated (ipsilateral) hand (CRST):**<br>■ ***Baseline***: 13.9; 95% CI: 12.0-15.7<br>■ ***3 months***: 95% CI: 0.2-18.6% → n.s. red. by 9.4%<br>■ ***6 months***: NR<br>■ ***12 months***: 95% CI: −0.4-18.5% → n.s. red. by 9.0%<br>**Postural tremor of the contralateral (treated) hand (CRST):**<br>■ ***Baseline***: NR<br>■ ***3 months***: [95% CI: 56.8%-81.8% → **s.s.** red. by 69.3%<br>■ ***6 months***: [95% CI: 52.8%-80.1%] → **s.s.** red. by 66.4%<br>■ ***12 months***: [95% CI: 51.9%-79.5%] → **s.s.** red. by 65.7%<br>**Tremor severity (CRST):**<br>■ ***Baseline***: 48.7 [95% CI: 44.3-53.05]<br>■ ***3 months***: 28 [95% CI: 23.2-32.8; **p<.001**] → red. by 43.6%<br>■ ***6 months***: NR<br>■ ***12 months***: 28.5 [95% CI: 23.6-33.3; **p<.001**] → red. by 42.8% | NR |
| **Functional disability**<br>**(mean (95% CI); p-value) [26]**<br>**or mean±SD; p-value [27]** | **Functional disability (part C of the CRST):**<br>■ ***Baseline***: 13.5 (95% CI: 12.0-14.9)<br>■ ***3 months***: 5.4 (95% CI: 3.9-6.9) → red. by 58.6% (95% CI: 48.0% 69.2%; **p<.001**)<br>■ ***6 months***: NR<br>■ ***12 months***: 5.7 (95% CI: 4.1-7.4) → red. by 56.4% (95% CI: 45.4%-67.3%; **p<.001**) | **Executive function (FAB):**<br>■ Baseline: 15.05±3.01<br>■ 6-month FU: 15.31±2.90<br>■ p=0.419 |
| **Health-related quality of life**<br>**(mean (95% CI); p-value) [26]**<br>**or mean±SD; p-value [27]** | **Quality of life (QUEST):**<br>■ ***Baseline***: 32.4 [95% CI: 26.1-58.8]<br>■ ***3 months***: 18.5 [95% CI: 12.7-24.2] → red. by 38.9%<br>■ ***6 months***: NR<br>■ ***12 months***: 17.4 [95% CI: 12.1-22.7] → red. by 46.3% | **Quality of life (QUEST):**<br>■ Baseline: 36.14±12.91<br>■ 6-month FU: 5.14±6.90<br>■ **p<0.001** |
| **Global assessment**<br>**of the disease symptoms** | NR | NR |
| **Length of hospital stay** | NR | NR |

| Author, year | Abe 2021 [26] | Saporito 2022 [27] |
|---|---|---|
| **Outcomes** | | |
| **Safety** | | |
| **Adverse events (n (%) [26] or % [27])** | *Most often*[77] *occurred gait disturbance 8 (22.9%), numbness/tingling 6 (17.1%), hemiparesis 5 (14.3%), unsteady gait 5 (14.3%). 77.3% of AEs were resolved within the 1. month.*<br>**Incidence (n (%)) of pts**[78]**:**<br>*Hemiparesis:* 5 (14.3%)<br>*Dysarthria:* 3 (8.6%)<br>*Dysphagia:* 1 (2.9%)<br>*Gait disturbance*: 8 (22.9%)<br>*Unsteady Gait*: 5 (14.3%)<br>*Hypotonia*: 3 (8.6%)<br>*Imbalance*: 1 (2.9%)<br>*Numbness/tingling*: 6 (17.1%)<br>*Peripheral neuropathy*: 2 (5.7%)<br>*Worsening of tinnitus*: 1 (2.9%)<br>*Weakness*: 1 (2.9%)<br>*Worsening of tremor*: 1 (2.9%)<br>*Heavy head*: 1 (2.9%)<br>*Scalp pain*: 2 (5.7%)<br>*Facial oedema*: 2 (5.7%)<br>*Dizziness*: 2 (5.7%)<br>77.3% of AEs were resolved within the 1.m. | ***MRI/ultrasound-related*** *(most often dizziness (21.5% ), scalp burning (16.4%) and nausea (8.4%)) and* ***thalamotomy-related*** *(most frequently contralateral weakness (7.5%)) occurred.*<br>**Procedure-related AEs:**<br>*MRI/ultrasound-related*:<br>■ Dizziness (21.5%[79])<br>■ Scalp burning (16.4%)<br>■ Nausea (8.4%)<br>■ Headache (6.2%)<br>■ Vagal reaction (2.5%)<br>*Thalamotomy-related:*<br>■ Contralateral weakness (3 (7.5%))<br>■ Dysgeusia (1 (2.5%))<br>■ Gait instability (1 (2.5))[80] |
| **Serious adverse events (n (%))** | 0 (0) | 0 (0) |

*Abbreviations: ET – essential tremor. AEs – adverse event. CRST – Clinical Rating Scale for Tremor. d – day(s). FAB – Frontal Assessment Battery. FU – follow-up. m – month(s). MMSE – Mini Mental State Examination. MOCA – Montreal Cognitive Assessment. n.s. – non-significant. NR – not reported. pts – patients. QUEST – Quality of life in Essential Tremor Questionnaire. red. – reduction. s.s. – statistically significant. tcMRgFUS – transcranial magnetic resonance-guided focused ultrasound. y – years.*

[77] i.e. the four most-frequently occurred events

[78] All adverse events occurred within the first six months.

[79] In the study text is stated "21.52.5%".

[80] With a gradual improvement the three months following tcMRgFUS thalamotomy

# Risk of bias tables and GRADE evidence profile

Two independent researchers judged the internal validity of the included studies. In case of disagreement, a third researcher was involved in solving the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the AIHTA [58] and in the Guidelines of EUnetHTA [38].

*Table A-4: Risk of bias – study level (Cochrane collaboration tool version 2 for randomised studies), see [20]*

| Trial | Bias arising from the randomisation process | Bias due to deviations from intended interventions | Bias due to missing outcome data | Bias in measurement of the outcome | Bias in selection of the reported result | Overall risk of bias |
|---|---|---|---|---|---|---|
| Elias 2016 [15] | Low[81] | Low[82,83] | Low[84] | Some concerns[85] | Low | Some concerns[86] |

[81] Randomisation is accomplished using a central computerised system.

[82] At the 3-month planned analysis, 86% and 95% of the patients guessed correctly the actual treatment assigned in the IG and CG, respectively.

[83] For the long-term follow-up results, the risk of bias is ”High”, as approximately 100% crossed-over from the CG to the IG, thereafter, all patients and assessors became unblinded.

[84] Applicable to 3-month blinded study period. Long-term follow-up results are affected by substantial bias due to missing data (1-yr : 7.8%; 2 yr: 11.8%; 3-yr: 31.5%).

[85] At the 3-month planned analysis, the assessors correctly guessed the actual treatment assigned for 70%, and 75% of the patients in the IG and CG, respectively.

[86] For the long-term follow-up results, the risk of bias is ”high”.

*Table A-5: Risk of bias – study level (The Risk Of Bias In Non-randomised Studies – of Interventions (ROBINS-I) assessment tool for comparative cohort studies comparing tcMRgFUS versus deep brain stimulation or radiofrequency thalamotomy), see [37, 38]*

| Study reference/ID | Bias due to confounding | Bias selection of participants into the study | Bias in measurement of intervention | Bias due to departures from intended interventions | Bias due to missing data | Bias in measurement of outcomes | Bias in selection of the reported results | Overall bias | Comments |
|---|---|---|---|---|---|---|---|---|---|
| **Huss 2015 [35]** | Serious[87] | Serious[88] | Serious[89] | Moderate[90] | Critical[91] | Serious[92] | Low | **Critical** | - |
| **Kim 2017 [36]** | Critical[93] | Critical[94] | Moderate[95] | Low | Serious[96] | Moderate[97] | Moderate[98] | **Critical** | - |

[87] Potential for confounding of the effect of intervention: Intervention discontinuations were not clearly assessable. The likelihood increased due to the retrospective study design. Authors did not use an appropriate analysis method that controlled for all the important confounding domains. No adjustment for potential confounders was conducted.

[88] Selection of participants for the study was not based on participant characteristics observed after the start of intervention. "Ninety-seven patients with ET were evaluated and treated with DBS or FUS at the University of Virginia between January 2004 and July 2013 by a single neurosurgeon."

[89] Intervention groups was not clearly defined. Classification of intervention status could have been affected by knowledge of the outcome or risk of the outcome.

[90] Deviations from the intended intervention beyond what would be expected in usual practice were not assessable due to the retrospective study design.

[91] Participants were excluded due to missing data on intervention status and on other variables needed for the analysis. There was 14% loss to FU. "Twelve patients, all of whom were treated with DBS, with missing information or incomplete evaluations were excluded from the analysis." "For unilateral DBS procedures, too few patients had preoperative and postoperative QUEST scores, so these patients were excluded from analysis of QUEST outcomes." Furthermore, the proportion of participants and reasons for missing data across interventions are not similar across the interventions. There is no evidence reported that results were robust to the presence of missing data.

[92] In this retrospective study, "patients and assessors were not blinded to treatment, which could have resulted in reporting or observational biases."

[93] Potential for confounding of the effect of intervention. Not clearly assessable if intervention discontinuations or switches were likely to be related to factors that are prognostic for the outcome. However, the likelihood increased due to retrospective study design. No appropriate analysis method controlled for all the important confounding domains used. No adjustment for potential confounders was conducted.

[94] Due to the retrospective analysis difficult to assess. However, data were collected before beginning of the study. "Unilateral RF thalamotomy procedures were only performed until 2004." DBS and tcMRgFUS patients "who underwent treatment between 2012 and 2014 were included in the analysis." No adjustment techniques used that are likely to correct for the presence of selection biases.

[95] No information if information used to define intervention groups was recorded at the start of the intervention.

[96] No exact outcome data was reported (e.g. mean, SD, 95% CI). Participants were excluded due to missing data on intervention status and on other variables needed for the analysis. Proportion of participants and reasons for missing data not similar across interventions. No clear evidence given that results were robust to the presence of missing data.

[97] No information was given if outcome measures have been influenced by knowledge of the intervention received and if outcome assessors were aware of the intervention received by study participants. Methods of outcome assessment not comparable across intervention groups.

[98] The reported effect estimate is only partly likely to be selected on the basis of the results from multiple outcome measurements within the outcome domain. However, data were Bonforroni corrected.

*Table A-6: Risk of bias – study level (case series), see [59]*

| Study reference/ID | Abe 2021 [26] | Saporito 2022 [27] |
|---|---|---|
| **Study objective** | | |
| 1. Was the hypothesis/aim/objective of the study clearly stated? | Yes | Yes |
| **Study design** | | |
| 2. Was the study conducted prospectively? | Yes | Yes |
| 3. Were the cases collected in more than one centre? | Yes | Unclear[99] |
| 4. Were patients recruited consecutively? | Yes[100] | Yes |
| **Study population** | | |
| 5. Were the characteristics of the patients included in the study described? | Yes | Yes |
| 6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated? | Yes | Yes |
| 7. Did patients enter the study at a similar point in the disease? | Yes | Yes |
| **Intervention and co-intervention** | | |
| 8. Was the intervention of interest clearly described? | Yes | Yes |
| 9. Were additional interventions (co-interventions) clearly described? | Partial[101] | No[102] |
| **Outcome measures** | | |
| 10. Were relevant outcome measures established a priori? | Yes | Yes |
| 11. Were outcome assessors blinded to the intervention that patients received? | Unclear[103] | Unclear[103] |
| 12. Were the relevant outcomes measured using appropriate objective/subjective methods? | Yes | Yes |
| 13. Were the relevant outcome measures made before and after the intervention? | Yes | Yes |
| **Statistical Analysis** | | |
| 14. Were the statistical tests used to assess the relevant outcomes appropriate? | Yes | Yes |

[99] No information was provided. However, we can only assume that it was a single-centre study as the Internal Review Board was from one hospital/university.

[100] Based on the description, we can assume that patients were consecutively enrolled. However, it was not stated specifically.

[101] Sedatives were allowed, although patients had to remain responsive during the procedure.

[102] It is not described if additional interventions (co-interventions) were performed.

[103] No information was provided if outcome assessors were blinded to the intervention that patients received.

| Study reference/ID | Abe 2021 [26] | Saporito 2022 [27] |
|---|---|---|
| **Results and Conclusions** | | |
| 15. Was follow-up long enough for important events and outcomes to occur? | Yes | Yes |
| 16. Were losses to follow-up reported? | Yes[104] | Yes |
| 17. Did the study provided estimates of random variability in the data analysis of relevant outcomes? | Yes | Yes |
| 18. Were the adverse events reported? | Yes | Yes |
| 19. Were the conclusions of the study supported by results? | Yes | Yes |
| **Competing interests and sources of support** | | |
| 20. Were both competing interests and sources of support for the study reported? | Yes | Yes |
| **Overall Risk of bias** | **Total Score: 19, Low risk** | **Total Score: 18, Moderate risk** |

[104] All cases were followed-up for 1 year; no losses to follow-up.

*Table A-7:* ***TcMRgFUS vs sham procedure:*** *Evidence profile for efficacy and safety in patients with drug-resistant essential tremor not eligible or not yet eligible for deep brain stimulation*

| Certainty assessment | | | | | | | Summary of findings | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| N of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | N of analysed patients | | Effect | Certainty |
| | | | | | | | tcMRgFUS | Sham | | |
| **Efficacy: Tremor severity (measured at 3m; no comparative data for long-term FUs)** | | | | | | | | | | |
| 1 | RCT | serious[a] | not serious | not serious | not serious | none | 56 | 20 | red. by 47% vs 0.1%<br>from 18.1±4.8 to 9.6±5.1 vs from 16.0±4.4 to 15.8±4.9<br>**p<0.001** | Moderat<br>⊕⊕⊕◯ |
| **Safety: Adverse events (3-12m)** | | | | | | | | | | |
| 1 | RCT | serious[a] | not serious | not serious | not serious | none | 56 | 20 | ***Comparative (at 3m):***<br>*tcMRgFUS vs sham: e.g.*[105] *paresthesia/numbness 14 vs 1 (25 vs 5%), gait disturbance 9 vs 1 (16 vs 5%), limb dysmetria 5 vs 0 (9 vs 0%), disequilibrium sensation 3 vs 0 (5 vs 0%)*<br>**Non-comparative:**<br>*E.g. paresthesias/numbness 21 (38%), gait disturbance 20 (36%), head discomfort 17 (30%), vertigo 12 (21%)* | Moderat<br>⊕⊕⊕◯ |
| 2 | PCSs | serious[b] | not serious | not serious | not serious | none | 35 | | *E.g. gait disturbance 8 (22.9%), numbness/tingling 6 (17.1%), hemiparesis 5 (14.3%), unsteady gait 5 (14.3%). 77.3% of AEs were resolved within the 1. month.* | ⊕◯◯◯<br>Very low |
| | | | | | | | 40 | | **MRI/ultrasound-related**<br>*e.g. dizziness (21.5% ), scalp burning (16.4%), nausea (8.4%)) and* **thalamotomy-related** *(e.g. contralateral weakness (7.5%) AEs occurred.* | |
| **Safety: Serious adverse events (3-12m)** | | | | | | | | | | |
| 1 | RCT | serious[a] | not serious | not serious | not serious | none | 56 | 20 | **Non-comparative data:** *dense and permanent hypesthesia of the dominant thumb and index finger: 1 (1.7%)* | Moderat<br>⊕⊕⊕◯ |
| 2 | PCSs | serious[b] | not serious | not serious | not serious | none | 35 | | 0 (0) | ⊕◯◯◯<br>Very low |
| | | | | | | | 40 | | 0 (0) | |

*Abbreviations: AEs – adverse events. FU – follow-up. m – months. n – number of patients. PCSs – prospective cohort studies. RCT – randomised controlled trial. red – reduction. RoB – risk of bias. SD – standard deviation. tcMRgFUS – transcranial magnetic resonance-guided high-intensity focused ultrasound. vs – versus. yr – year(s).*

*Comments:*

[a] *Using the Cochrane Collaboration tool version 2, 1 RCT with some concerns arising from bias in measurement of the outcome for the 3-month period. For the long-term FU results, the RoB is "High", as approximately 100% crossed-over from the CG to the IG, thereafter, all patients and assessors became unblinded. Long-term FU results are affected by substantial bias due to missing data (1-yr : 7.8%; 2 yr: 11.8%; 3-yr: 31.5%).*

[b] *Using the IHE checklist, 1 study (non-comparative study) with moderate RoB arising from not clearly describing additional interventions (co-interventions) and 1 study (non-comparative study) with low RoB.*

*Nomenclature for GRADE table:*

*Limitations: 0: no limitations or no serious limitations; -1: serious limitations*

*Inconsistency: NA: Not applicable (only one trial); 0: no important inconsistency; -1: important inconsistency*

*Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty*

*Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)*

[105] The four most often occurring events are reported for all studies.

*Table A-8:* ***TcMRgFUS vs deep brain stimulation or radiofrequency thalamotomy:***
*Evidence profile for efficacy and safety in patients with drug-resistant essential tremor eligible for deep brain stimulation*

| Certainty assessment | | | | | | | Summary of findings | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| N of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | N of analysed patients | | Effect | Certainty |
| | | | | | | | tcMRgFUS | DBS or RF | | |
| **Efficacy: Tremor severity (measured at 1-13m)** | | | | | | | | | | |
| 2 | Comparative cohort studies | very serious[a] | not serious | not serious | serious[106] | none | 15 | 13 vs 57 | **Pre:** 54.9 vs 59.5 vs 64.4<br>**Post:** 17.7 (55.7) vs 15.8 (62.8) vs 13.2 (79.5)<br>All 3 groups: **s.s.** from baseline<br>IG vs CGb: **s.s.** | ⊕◯◯◯ Very low |
| | | | | | | | 23 | 19 vs 17 | **1m:** 21 (91.3) vs 17 (89.5) vs 17 (100)<br>**12m:** 18 (78.3) vs 16 (84.2) vs 12 (70.6)<br>n.s.[107] | |
| **Safety: Adverse events (measured at 1-13m)** | | | | | | | | | | |
| 2 | Comparative cohort studies | very serious[a] | not serious | not serious | not serious | none | 15 | 13 vs 57 | *AEs include a variety of neurologic, physical and hardware-related events as well as haemorrhage.*<br>*3m: Less* **haemorrhage** *in the tcMRgFUS group. TcMRgFUS patients had tendentially more* **physical** *events resolved at the 12-month FU.*<br>*12m: TcMRgFUS patients generally had less* **neurologic** *and* **hardware-related** *events than DBS, except for paresthesia.* | ⊕◯◯◯ Very low |
| | | | | | | | 23 | 19 vs 17 | ***1m:*** 3 (13.0) vs 1 (5.3) vs 10 (58.8)<br>***12m:*** 1 (4.4) vs 4 (21.1) vs 2 (11.8) | |
| 2 | PCSs | serious[b] | not serious | not serious | not serious | none | 35 | - | *E.g.*[108] *gait disturbance 8 (22.9%), numbness/tingling 6 (17.1%), hemiparesis 5 (14.3%), unsteady gait 5 (14.3%). 77.3% of AEs were resolved within the 1. month.* | ⊕◯◯◯ Very low |
| | | | | | | | 40 | - | **MRI/ultrasound-related** *(e.g. dizziness (21.5% ), scalp burning (16.4%), nausea (8.4%))* and **thalamotomy-related** *(e.g. contralateral weakness (7.5%)) AEs occurred.* | |
| **Safety: Serious adverse events** | | | | | | | | | | |
| 2 | PCSs | serious[b] | not serious | not serious | not serious | none | 35 | - | 0 (0) | ⊕◯◯◯ Very low |
| | | | | | | | 40 | - | 0 (0) | |

*Abbreviations: DBS – deep brain stimulation. M – months. N – number of patients. n.s. – not statistically significant (p>0.05). PCSs – prospective cohort studies. RoB – risk of bias. RF – radiofrequency thalamotomy. s.s. – statistically significant (p<0.05). tcMRgFUS – transcranial magnetic resonance-guided high-intensity focused ultrasound. vs – versus.*

[106] Optimal information size not met.

[107] Between-group differences at 1 month and 12 months.

[108] The four most often occurring events are reported for all studies.

*Comments:*

[a] *Using the ROBINS-I checklist, 1 study (comparative cohort study) with critical RoB mainly arising from bias due to missing data, but also from bias due to confounding, bias selection of participants into the study, bias in measurement of intervention, and bias in measurement of outcomes. 1 study (comparative cohort study) with critical RoB mainly arising from bias due to confounding and bias selection of participants into the study, but also from bias due to missing data.*

[b] *Using the IHE checklist, 1 study (non-comparative study) with moderate RoB arising from not clearly describing additional interventions (co-interventions) and 1 study (non-comparative study) with low RoB.*

*Nomenclature for GRADE table:*

*Limitations: 0: no limitations or no serious limitations; -1: serious limitations*

*Inconsistency: NA: Not applicable (only one trial); 0: no important inconsistency; -1: important inconsistency*

*Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty*

*Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)*

# Applicability table

*Table A-9: Summary table characterising the applicability of a body of studies*

| Domain | Description of applicability of evidence |
|---|---|
| **Population** | Within the included studies, both patient populations (patients who are eligible for DBS and those who are not eligible for BDS) were covered by one RCT, two comparative cohort studies, and two prospective non-comparative studies. The inclusion criteria of these studies reflect the intended patient population for the technology. Moreover, the patient populations of included studies reflect real-world conditions concerning age, sex, disease duration, and underlying drug-resistant ET. |
| **Intervention** | Included studies evaluated the transcranial magnetic resonance-guided high-intensity focused ultrasound thalamotomy (unilateral) produced by one manufacturer. Device generations used do not vary between the studies (i.e. model 4000). |
| **Comparators** | Bilateral or unilateral thalamic DBS, RF thalamotomy, and sham procedure are used as comparators in the included comparative studies. In one of the two included comparative cohort studies [35], DBS is the comparator which is recommended in clinical guidelines for patients who are eligible for DBS, and for those who are not eligible for DBS, sham procedure is considered a comparator of choice as reported in the RCT [15]. However, the other comparative cohort study [36], RF thalamotomy, which is not recommended by clinical practice guidelines, was one of the comparators in addition to DBS; this may hinder the applicability of this study's results. |
| **Outcomes** | For efficacy outcomes, the critical outcome tremor severity was reported in all included studies except in one of the prospective non-comparative studies [27]. This outcome was reported as the primary outcome measure in only two of the five included studies [15, 26]. On the other hand, the other three studies [27, 35, 36] did not state any primary outcomes. This may minimise the study results' applicability, especially since their power is not calculated in any of these three studies.<br>Regarding safety outcomes, the critical outcome of AEs was reported in all included studies, whereas the critical outcome of SAEs was reported in three of the five studies. |
| **Setting** | The included RCT was conducted as multicentre studies in different geographical regions (United States, Canada, Japan, South Korea). The two included comparative cohort studies were conducted in the United States and South Korea, whereas the two prospective non-comparative studies were conducted in Japan and Italy. For example, in the Japanese population, the skull density ratio is lower (≥0.30) than in the US population (≥0.45). Many US centres screen out candidates with a skull density ratio <0.40, as a low skull density ratio is associated with increased difficulty focusing the ultrasound beams and achieving therapeutic temperatures at the target [55]. However, tcRMgFUS is effective and safe also in this population [24], and the indications for tcMRgFUS could be expanded to include ET patients with a low skull density ratio [60]. It might be that geographic settings limit the applicability of the results. |

# List of ongoing randomised controlled trials

*Table A-10: List of ongoing randomised controlled trials of transcranial magnetic resonance-guided high-intensity focused ultrasound*

| Identifier/ Trial name | Patient population | Intervention | Comparison | Primary Outcome | Primary completion date | Sponsor |
|---|---|---|---|---|---|---|
| JPRN-UMIN000010714 | (n=10)<br>1. Men and women, ≥22 years<br>2. Tremor refractory to adequate trials of at least two medications<br>3. Significant disability due to essential tremor despite medical treatment | ExAblate Transcranial: Focused ultrasound | Sham | 1. Tremor improvement<br>2. Evaluation of adverse effect | NR[109] | Tokyo Women's Medical University Shin-yurigaoka General Hospital.<br>Funded by InSightec Ltd. |

[109] Date of completion is not reported in this database.

# Literature search strategies

## Search strategy for Cochrane

| Search Name: Transcranial HIFU for Essential Tremors | |
|---|---|
| Last Saved: 21/12/2022 14:17:19 | |
| Comment: MEL2023 (LG/R) | |
| ID | Search |
| #1 | MeSH descriptor: [Essential Tremor] explode all trees |
| #2 | (essential NEAR tremor*) (Word variations have been searched) |
| #3 | #1 OR #2 (Word variations have been searched) |
| #4 | MeSH descriptor: [Ultrasonic Therapy] explode all trees |
| #5 | MeSH descriptor: [Ultrasonography, Interventional] explode all trees |
| #6 | MeSH descriptor: [Magnetic Resonance Imaging, Interventional] explode all trees |
| #7 | (ultrasound*) (Word variations have been searched) |
| #8 | #4 OR #5 OR #6 OR #7 (Word variations have been searched) |
| #9 | ("high intensit*" OR HIFU) (Word variations have been searched) |
| #10 | #8 AND #9 (Word variations have been searched) |
| #11 | (thalamotom*) (Word variations have been searched) |
| #12 | (thalam* NEAR ablat*) (Word variations have been searched) |
| #13 | #11 OR #12 (Word variations have been searched) |
| #14 | #7 AND #13 (Word variations have been searched) |
| #15 | ((transcrani* OR trans-crani*) NEAR ("high intensity focused ultrasound" OR HIFU OR mrgfus* OR thalam*)) (Word variations have been searched) |
| #16 | (tcMRgFUS) (Word variations have been searched) |
| #17 | (Exablate) (Word variations have been searched) |
| #18 | #10 OR #14 OR #15 OR #16 OR #17 (Word variations have been searched) |
| #19 | #3 AND #18 (Word variations have been searched) |
| #20 | (conference proceeding):pt |
| #21 | (abstract):so |
| #22 | (clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so |
| #23 | #20 OR #21 OR #22 |
| #24 | #19 NOT #23 |
| Total hits: 15 | |

## Search strategy for Embase

| Search Name: Transcranial HIFU for Essential Tremors | | |
|---|---|---|
| Search date: 21.12.2022 | | |
| No. | Query Results | Results |
| #24. | #22 NOT #23 | 456 |
| #23. | #22 AND 'Conference Abstract'/it | 190 |
| #22. | (#17 OR #18 OR #19 OR #20) AND ([english]/lim OR [german]/lim) | 646 |
| #21. | #17 OR #18 OR #19 OR #20 | 658 |
| #20. | tcmrgfus | 87 |
| #19. | (transcrani* OR 'trans-crani*') NEAR/5 ('high intensity focused ultrasound' OR hifu OR mrgfus* OR thalam*) | 170 |
| #18. | 'transcranial magnetic resonance guided focused ultrasound'/exp | 78 |

| | | |
|---|---|---|
| #17. | #3 AND #16 | 456 |
| #16. | #4 OR #5 OR #6 OR #12 OR #15 | 8,854 |
| #15. | #13 OR #14 | 444 |
| #14. | exablate | 444 |
| #13. | 'exablate'/exp | 17 |
| #12. | #10 AND #11 | 522 |
| #11. | ultrasound* | 616,520 |
| #10. | #7 OR #8 OR #9 | 2,727 |
| #9. | thalam* NEAR/5 ablat* | 156 |
| #8. | thalamotom* | 2,589 |
| #7. | 'thalamotomy'/exp | 2,041 |
| #6. | hifu | 4,883 |
| #5. | 'high intensit* focus* ultrasound*' | 7,630 |
| #4. | 'high intensity focused ultrasound'/exp | 6,519 |
| #3. | #1 OR #2 | 8,791 |
| #2. | essential NEAR/2 tremor* | 8,791 |
| #1. | 'essential tremor'/exp | 7,377 |

## Search strategy for Medline via Ovid

| Search Name: Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to December 19, 2022>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <2018 to December 19, 2022> | |
|---|---|
| Search date: 20.12.2022 | |
| ID | Search |
| 1 | exp Essential Tremor/ (3569) |
| 2 | (essential adj3 tremor*).mp. (6842) |
| 3 | 1 or 2 (6842) |
| 4 | exp Ultrasonic Therapy/ (16440) |
| 5 | ultrasound*.mp. (415913) |
| 6 | "therapeutic use".fs. (2847259) |
| 7 | 5 and 6 (20531) |
| 8 | 4 or 7 (35668) |
| 9 | (high intensity or HIFU).mp. (51907) |
| 10 | 8 and 9 (4669) |
| 11 | thalamotom*.mp. (1655) |
| 12 | (exp Thalamus/ or thalamus.mp.) adj2 ablat*.mp. (229) |
| 13 | 11 or 12 (1863) |
| 14 | 5 and 13 (467) |
| 15 | ((transcrani* or trans-crani*) adj5 (high intensity focused ultrasound or HIFU or mrgfus* or thalamotom*)).mp. (125) |
| 16 | tcMRgFUS.mp. (94) |
| 17 | 10 or 14 or 15 or 16 (5157) |
| 18 | 3 and 17 (434) |
| 19 | limit 18 to (english or german) (423) |
| 20 | remove duplicates from 19 (237) |

## Search strategy for HTA-INATHTA

| Search Name: Transcranial HIFU for Essential Tremors | |
|---|---|
| Search date: 21.12.2022 | |
| ID | Search query,"Hits","Searched At" |
| 6 | ((ultrasound* thalam*) OR (tcMRgFUS) OR (transcranial HIFU) OR (transcranial ultrasound)) AND (English OR German)[Language],"8","2022-12-21T14:47:48.000000Z" |
| 5 | (ultrasound* thalam*) OR (tcMRgFUS) OR (transcranial HIFU) OR (transcranial ultrasound),"8","2022-12-21T14:45:20.000000Z" |
| 4 | ultrasound* thalam*,"1","2022-12-21T14:41:19.000000Z" |
| 3 | tcMRgFUS,"1","2022-12-21T14:40:08.000000Z" |
| 2 | transcranial HIFU,"0","2022-12-21T14:39:43.000000Z" |
| 1 | transcranial ultrasound,"7","2022-12-21T14:38:51.000000Z" |
| Total hits: 8 | |

**HTA Austria**
Austrian Institute for
Health Technology Assessment
GmbH