Norwegian Medical Products Agency

Single Technology Assessment

Magnetic resonance-guided high-intensity focused ultrasound for treatment of essential tremor

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Executive summary

Introduction

Essential tremor (ET) is a neurological disorder characterised by involuntary rhythmic shaking of one or more body parts (that is not caused by other known conditions). First-line treatment for moderate to severe ET involves pharmaceutical interventions. About half the patients do not respond satisfactorily to pharmaceutical treatment, and these may be offered deep brain stimulation (DBS). DBS involves surgical implantation of electrodes inside the brain, and many patients are ineligible or unwilling to undergo DBS. Magnetic Resonance-guided Focused Ultrasound (MRgFUS) uses high-intensity focused ultrasound to create a permanent lesion in the part of thalamus that causes tremor. The lesion is created by thermal heating and the treatment is monitored by MR imaging.

Objective

The objective of the current single technology assessment (STA) was to investigate the clinical effect and safety of unilateral MRgFUS for patients with medication-refractory, moderate to severe ET who are ineligible or unwilling to undergo DBS. Additionally, to investigate the cost-effectiveness of unilateral MRgFUS compared to no procedure, and budget impacts of implementing MRgFUS in Norway. The STA is an appraisal of documentation submitted by Insightec.

Method

Clinical effect and safety: The submitter performed a systematic literature search and identified both randomised and non-randomised studies. We performed a separate search to evaluate whether all relevant studies were included. We extracted data from the included studies and calculated effect estimates and weighted averages. We critically appraised the risk of bias and assessed our confidence in the results using the GRADE approach.

Health economic assessment: The submitter provided a health economic model which combined a decision tree and a Markov model to capture life-time quality-adjusted life-years (QALY) and costs for patients undergoing unilateral MRgFUS, compared to no procedure. The submitter also performed sensitivity analyses and a budget impact analysis. We appraised the model and made some revisions to the analyses.

Results

Clinical effect and safety: One multicenter RCT with 76 patients and 13 non-randomised studies with 1029 patients (in total) were included. All studies investigated patients with medication-refractory, moderate to severe ET. The RCT compared unilateral MRgFUS with sham (placebo), and the non-randomised studies compared pre- and posttreatment scores (no control group). MRgFUS-treated patients showed lower hand tremor and disability scores, and probably improved quality of life compared to sham patients, three months after the treatment (Summary of findings table below). It was hard to judge the duration of the treatment effect based on the available documentation. Non-randomised studies indicated that the beneficial treatment effects persist one year after treatment, but our certainty in these results was low. Some non-randomised studies also suggested that treatment effects may persist substantially beyond one year but observed a trend towards reduced treatment effect with time (very low certainty). MRgFUS was also associated with adverse events. The adverse events were common, but mostly mild and transient. The most common adverse events were “paresthesia or numbness” and “gait disturbance”. These events occurred in more than one third of the patients and persisted one year after the treatment in about one tenth of the patients.

Summary of findings table

Outcome	Expected absolute or relative effects (95% CI)		Number of patients (studies)	Certainty (GRADE)	Comments
	Sham	Unilateral MRgFUS			
3 months					
Hand tremor score	**15.8**	MD **6.2 lower** (8.7 to 3.7 lower)	**76** (1 RCT)	⊕⊕⊕⊕ High	7 non-RCT (n = 515) reported the outcome, all agreed with RCT
Disability score	**15.6**	MD **9.4 lower** (11.9 to 7.0 lower)	**76** (1 RCT)	⊕⊕⊕⊕ High	4 non-RCT (n = 294) reported the outcome, all agreed with RCT
Quality of life	**41.4**	MD **18.3 lower** (27.9 to 8.7 lower)	**76** (1 RCT)	⊕⊕⊕◯ Moderate [a]	3 non-RCT (n = 110) reported the outcome, all agreed with RCT
12 months					
Hand tremor score	**NA**	**66.2% lower *** (58.7 to 73.6%)	**346** (8 non-RCT)	⊕⊕◯◯ Low [b]	
Disability score	**NA**	**66.8% lower *** (48.2 to 77.3%)	**142** (3 non-RCT)	⊕⊕◯◯ Low [b]	
Quality of life	**NA**	**53.7% lower *** (46.8 to 60.6%)	**183** (5 non-RCT)	⊕⊕◯◯ Low [b]	
36 months					
Hand tremor score	**NA**	**57.1% lower *** (39.6 to 74.5%)	**68** (3 non-RCT)	⊕◯◯◯ Very low [b,c]	
Disability score	**NA**	**56.1% lower *** (NA)	**52** (1 non-RCT)	⊕◯◯◯ Very low [b,c]	
Quality of life	**NA**	**43.6% lower *** (30.1 to 57.0%)	**68** (3 non-RCT)	⊕◯◯◯ Very low [b,c]	

Hand tremor score was assessed by Clinical Rating Scale for Tremor (CRST) part A and B, disability score was assessed by CRST part C, and quality of life was assessed by the Quality of Life in Essential Tremor (QUEST). Lower scores indicate less severe tremor, for all scales. Our certainty of the evidence was downgraded because: **a,** the confidence interval was wide and included small and large effects; **b**, the included studies had high risk of bias.; **c**, high number of missing patients (drop-outs).
Abbreviations: CI, confidence interval; MD, mean difference; n, number of patients; NA, not applicable.
*****, posttreatment scores were compared to pretreatment scores in the non-randomised studies (relative effect in %).

Health economic assessment: In the analysis, unilateral MRgFUS generated more QALYs, but at a higher cost than no procedure. The ICER was approximately NOK 189,000 per QALY. Absolute shortfall (severity) was calculated to be 6.8 QALYs. The budget impact of implementing one MRgFUS device was estimated to be approximately NOK [redacted] million over five years. Budget impacts of introducing two devices was estimated to be around NOK [redacted] million over five years. In the analyses, the device cost is included the first year.

Patient perspective

The patient association "*Essensiell Tremor-Foreningen Norge"* answered a patient input questionnaire. The association emphasised that ET impacts all hand-related activities, and that medical treatments are inadequate for about half the patients. The association argued that MRgFUS offers considerable tremor reduction, and that the non-invasive nature and the minimal recovery time is highly advantageous.

Discussion

The included studies were conducted in USA, Canada, South Korea, Japan, Spain, Italy, China, Australia, Germany, and Israel. The included patients were comparable to the population that can be expected to undergo MRgFUS in Norway, and consequently the reported results should be relevant for Norway.

One multicenter RCT compared the effect of unilateral MRgFUS with that of sham. The RCT was well designed, and risks of bias were deemed to be low. Our certainty in the results was high and moderate, but it remains a weakness that only one RCT evaluated the effect of MRgFUS. We also included 13 non-randomised studies (without control group), and the results from these aligned well with the results from the RCT. This represents an important strength. The effect estimates beyond 3 months were based on non-randomised studies only. Our certainty in these results was low or very low because the design of these studies inherently caused high risk of bias (no control group). New well-designed studies that investigate the duration of the treatment effect are needed. The number of patients in the included RCT was based on a power analysis considering the effect on hand tremor score assessed in a prior pilot study. Accordingly, the number of patients was sufficient to detect significant differences in hand tremor score. The number of patients was also sufficient to identify several common adverse events. However, the study was not powered to identify adverse events that may occur rarely. Although most adverse events identified in the current report were mild and transient, we cannot rule out the possibility that MRgFUS may induce rare adverse events that can be severe.

The cost-effectiveness results remained robust in the sensitivity analyses. However, there is uncertainty associated with the duration of the treatment effect. There is also uncertainty related to the utilities applied, and the actual cost of the MRgFUS procedure, and other parameters in the health economic model.

There are organisational aspects that need to be considered before MRgFUS can be offered in Norway. Decision makers must decide about how many locations should offer MRgFUS. The submitter has assumed that 100 patients will be treated with MRgFUS yearly and suggested that two locations are appropriate. The investment costs of MRgFUS are high. One may consider only one location which would imply lower investment costs and a need for specially trained personnel in only one place. The treatment procedure is performed inside a MR-scanner and lasts 3–4 hours. Decision makers should also consider the need for MR capacity. Fifty full days of MR-scanning (two procedures per day) will be required to treat 100 patients per year.

Conclusion

Unilateral MRgFUS appeared to be an effective and safe treatment option for patients with medication-refractory, moderate to severe ET patients. Unilateral MRgFUS reduced hand tremor and disability, and probably improved quality of life three months after the treatment. The treatment effects may persist substantially longer, but the long-term effects were associated with low certainty. Adverse events were common, but mostly mild and transient. Studies with larger patient cohorts are needed to identify or rule out possible adverse events that may occur rarely.

The cost-effectiveness analysis indicated that unilateral MRgFUS generates more QALYs, but at a higher cost than no procedure. The estimated ICER was approximately NOK 189,000 per QALY. There is uncertainty associated with parameters in the model. Implementation of one MRgFUS device could entail budget impact of around NOK [redacted] million over five years, and implementation of two devices could entail budget impact of around NOK [redacted] million.

Sammendrag (Norwegian summary)

Innledning

Essensiell tremor (ET) er en nevrologisk lidelse som karakteriseres av ufrivillig rytmisk skjelving i en eller flere kroppsdeler (som ikke skyldes andre kjente tilstander). Førstelinje behandling for moderat til alvorlig ET er medikamentell behandling. Om lag halvparten av pasientene responderer ikke tilstrekkelig på medikamentell behandling og disse kan tilbys dyp hjernestimulering (DBS). DBS innebærer kirurgisk implantasjon av elektroder i hjernen. Mange pasienter kan eller vil ikke gjennomføre DBS. Magnetisk resonans-veiledet fokusert ultralyd (MRgFUS) bruker høyintensitets fokusert ultralyd til å lage en permanent lesjon (skade) i den delen av thalamus som gir tremor. Lesjonen lages ved å varme hjernevevet og behandlingen overvåkes med MR-avbildning.

Hensikt

Hensikten med metodevurderingen var å undersøke klinisk effekt og sikkerhet for unilateral (ensidig) MRgFUS for pasienter med behandlingsresistent, moderat til alvorlig ET som ikke kan eller ikke vil gjennomføre DBS. I tillegg, å undersøke kostnadseffektivitet ved unilateral MRgFUS sammenlignet med ingen prosedyre, og budsjettkonsekvenser ved å innføre MRgFUS i Norge. Metodevurderingen er basert på innsendt dokumentasjon fra Insightec.

Metode

Klinisk effekt og sikkerhet: Innsender gjennomførte et systematisk litteratursøk og identifiserte både randomiserte og ikke-randomiserte studier. Vi gjennomførte et eget søk for å vurdere om alle relevante studier var inkludert. Vi hentet data fra de inkluderte studiene og beregnet effektestimat og vektede gjennomsnitt. Vi vurderte risiko for systematiske skjevheter og vurderte vår tillit til resultatene med GRADE-tilnærmingen.

Helseøkonomisk vurdering: Innsender leverte en modell som kombinerte et beslutningstre og en Markov-modell for å beregne kvalitetsjusterte leveår og kostnader i en livslang tidshorisont. Modellen sammenlignet pasienter som fikk unilateral MRgFUS med pasienter som fikk ingen prosedyre. Innsender utførte også sensitivitetsanalyser og en budsjettkonsekvensanalyse. Vi vurderte modellen og gjorde noen endringer i analysene.

Resultater

Klinisk effekt og sikkerhet: Én multisenter RCT med 76 pasienter og 13 ikke-randomiserte studier med til sammen 1029 pasienter ble inkludert. Alle studiene undersøkte pasienter med behandlingsresistent moderat til alvorlig ET. RCT-en sammenlignet unilateral MRgFUS med sham (placebo), og de ikke-randomiserte studiene sammenlignet før- og etter score (ingen kontrollgruppe). MRgFUS-behandlede pasienter hadde lavere score for håndtremor og funksjonsnedsettelse, og trolig bedre livskvalitet enn sham-pasienter, tre måneder etter behandlingen (Oppsummeringstabell). Det var utfordrende å vurdere varigheten av behandlingseffekten basert på den tilgjengelige dokumentasjonen. Ikke-randomiserte studier indikerte at behandlingseffekten vedvarte ett år etter behandlingen, men tilliten vår til disse resultatene var lav. Enkelte ikke-randomiserte studier indikerte også at behandlingseffekten kan vare betydelig lengre enn ett år, men observerte at effekten avtok over tid (svært lav tillit). MRgFUS var også forbundet med uønskede hendelser. De uønskede hendelsene var vanlige, men for det meste milde og forbigående. De mest vanlige uønskede hendelsene var “parestesi eller nummenhet”, og gangforstyrrelser (“gait disturbance”). Disse effektene forekom hos over en tredjedel av pasientene, og vedvarte et år etter behandlingen hos om lag en tidel av pasientene.

Oppsummeringstabell

Utfall	Forventet absolutt eller relativ effekt (95 % KI)		Antall pasienter (studier)	Tillit til resultat (GRADE)	Kommentarer
	Sham	Unilateral MRgFUS			
3 måneder					
Håndtremor score	**15,8**	MD **6,2 lavere** (8,7 til 3,7 lavere)	**76** (1 RCT)	⊕⊕⊕⊕ Høy	7 ikke-RCT (n = 515) rapporterte utfallet, alle samstemte med RCT
Funksjons-nedsettelse	**15,6**	MD **9,4 lavere** (11,9 til 7,0 lavere)	**76** (1 RCT)	⊕⊕⊕⊕ Høy	4 ikke-RCT (n = 294) rapporterte utfallet, alle samstemte med RCT
Livskvalitet	**41,4**	MD **18,3 lavere** (27,9 til 8,7 lavere)	**76** (1 RCT)	⊕⊕⊕◯ Moderat [a]	3 ikke-RCT (n = 110) rapporterte utfallet, alle samstemte med RCT
12 måneder					
Håndtremor score	**NA**	**66,2 % lavere *** (58,7 til 73,6 %)	**346** (8 ikke-RCT)	⊕⊕◯◯ Lav [b]	
Funksjons-nedsettelse	**NA**	**66,8 % lavere *** (48,2 til 77,3 %)	**142** (3 ikke-RCT)	⊕⊕◯◯ Lav [b]	
Livskvalitet	**NA**	**53,7 % lavere *** (46,8 til 60,6 %)	**183** (5 ikke-RCT)	⊕⊕◯◯ Lav [b]	
36 måneder					
Håndtremor score	**NA**	**57,1% lavere *** (39,6 til 74,5%)	**68** (3 ikke-RCT)	⊕◯◯◯ Veldig lav [b,]	
Funksjons-nedsettelse	**NA**	**56,1% lavere *** (NA)	**52** (1 ikke-RCT)	⊕◯◯◯ Veldig lav [b,]	
Livskvalitet	**NA**	**43,6% lavere *** (30,1 til 57,0%)	**68** (3 ikke-RCT)	⊕◯◯◯ Veldig lav [b,c]	

Hånd-tremor score ble målt med Clinical Rating Scale for Tremor (CRST) del A and B, funksjonsnedsettelse ble målt med CRST del C, og livskvalitet ble malt med Quality of Life in Essential Tremor (QUEST). Lavere score innebærer mindre alvorlig tremor, for alle måleverktøyene. Vår tillit til resultatene ble nedgradert fordi: **a,** konfidensintervallene var brede og inkluderte små og store effekter; **b**, de inkluderte studiene hadde høy risiko for systematisk skjevhet; **c**, høyt frafall av pasienter.
Forkortelser: KI, konfidensinterval; MD, gjennomsnittlig differanse; n, antall pasienter; NA, ikke aktuelt.
*****, etter-behandling score ble sammenlignet med før-behandling score i ikke-randomiserte studier (relativ effekt i %).

Helseøkonomisk vurdering: I analysene genererte unilateral MRgFUS flere kvalitetsjusterte leveår, men til en høyere kostnad enn ingen prosedyre. Den inkrementelle kostnadeffektivitetsratioen var omtrent 189 000 kroner per vunnet kvalitetsjusterte leveår. Absolutt prognosetap (alvorlighet) ble beregnet til 6,8 kvalitetsjusterte leveår. Budsjettvirkninger ved å implementere ett MRgFUS-utstyr ble estimert til cirka [redacted] millioner kroner over fem år. Budsjettvirkningene ved å implementere to utstyr ble estimert til å være omtrent [redacted] millioner kroner over fem år. I analysene er kostnad for utstyret inkludert i det første året.

Pasientperspektiv

Pasientforeningen "*Essensiell Tremor-Foreningen Norge"* besvarte et spørreskjema om brukererfaringer. Foreningen framhevet at ET påvirker alle håndrelaterte aktiviteter, og at medikamentell behandling ikke er tilstrekkelig for omtrent halvparten av pasientene. Foreningen påpekte at MRgFUS kan redusere tremor betydelig, og at det er en stor fordel at metoden ikke krever operasjon og medfører minimal rekonvalenstid.

Diskusjon

De inkluderte studiene ble gjennomført i USA, Canada, Sør-Korea, Japan, Spania, Italia, Kina, Australia, Tyskland og Israel. Pasientene i studiene var sammenlignbare med populasjonen som kan være aktuell for MRgFUS-behandling i Norge. Resultatene fra studiene bør følgelig være relevante for Norge.

Én RCT sammenlignet effekten av unilateral MRgFUS med effekten av sham. RCT-en var godt designet, og risiko for systematisk skjevhet bel vurdert å være lav. Vår tillit til resultatene var høy og moderat, men det er en svakhet at det bare er en RCT som har undersøkt effekten av MRgFUS. Vi inkluderte også 13 ikke-randomiserte studier, og resultatene fra disse samsvarte godt med resultatene i RCT-en. Dette er en viktig styrke. Effektestimatene for langtidseffekt (mer enn tre måneder) var bare basert på ikke-randomiserte studier. Vår tillit til disse resultatene var lav eller svært lav fordi studiedesignet medførte høy risiko for systematisk skjevhet. Det er behov for nye godt designede studier som undersøker varigheten av behandlingseffekten. Antallet pasienter i den inkluderte RCT-en var basert på en styrkeberegning som brukte effekten på håndtremor fra en tidligere gjennomført pilotstudie. Følgelig var antallet pasienter tilstrekkelig stort til å detektere signifikante forskjeller i håndtremor score. Antallet pasienter var også tilstrekkelig til å identifisere flere uønskede hendelser som forekom ofte. Studien var imidlertid ikke styrkeberegnet for å identifisere sjeldne uønskede hendelser. Selv om de fleste uønskede hendelsene som ble identifisert i rapporten vår var milde og forbigående, kan vi ikke utelukke at MRgFUS kan føre til sjeldne uønskede hendelser som kan være alvorlige.

Resultatene fra kostnadseffektivitetsanalysen forble robuste i sensitivitetsanalysene. Imidlertid er det usikkerhet knyttet til varighet av behandlingseffekten. Det er også usikkerhet knyttet til nyttevektene som er brukt, den faktiske kostnaden ved MRgFUS-prosedyren og andre parametere i den helseøkonomiske modellen.

Det er organisatoriske aspekter som må vurderes før MRgFUS kan tilbys i Norge. Det må bestemmes hvor mange lokasjoner som skal tilby MRgFUS-behandling. Innsender har antatt at 100 pasienter vil få MRgFUS-behandling årlig og har foreslått at to lokasjoner kan være hensiktsmessig. Investeringskostnadene ved MRgFUS er høye. Man kan også vurdere bare én lokasjon noe som vil gi lavere investeringskostnader og behov for spesialkvalifisert personell på bare ett sted. Behandlingen gjennomføres i en MR-skanner og varer i 3-4 timer. Beslutningstakere må også vurdere behov for MR-kapasitet. Det vil være nødvendig med 50 fulle dager med MR-avbildning (to MRgFUS-prosedyrer per dag) for å behandle 100 pasienter per år.

Konklusjon

Unilateral MRgFUS fremstår som en effektiv og trygg behandling for pasienter med behandlingsresistent, moderat til alvorlig ET. Unilateral MRgFUS reduserte håndtremor og funksjonsnedsettelse, og forbedret trolig livskvalitet tre måneder etter behandling. Behandlingseffekten kan vare betydelig lengre, men resultatene for langtidseffekter var mer usikre. Uønskede hendelser forekom ofte, men var for det meste milde og forbigående. Det er behov for studier med større pasientkohorter for å identifisere eller utelukke mulige alvorlige hendelser som kan forekomme sjeldent.

Kostnadseffektivitetsanalysen indikerte at unilateral MRgFUS genererer flere kvalitetsjusterte leveår, men til en høyere kostnad enn ingen prosedyre. Den estimerte inkrementelle kostnadseffektivitetsratioen var omtrent 189 000 kroner per vunnet kvalitetsjusterte leveår. Det er knyttet usikkerhet til parametere i modellen. Budsjettvirkninger ved å innføre ett eller to MRgFUS-utsyr ble beregnet å være omtrent [redacted] og [redacted] millioner kroner over fem år.

Preface

The Division of Health Economics and Analysis at the Norwegian Medical Products Agency (NOMA) was commissioned to perform a single technology assessment of magnetic resonance guided high-intensity focused ultrasound for treatment of essential tremor. The single technology assessment was commissioned within the National System for Managed Introduction of New Health Technologies ("Nye metoder"). The assignment was originally given to the Norwegian Institute of Public Health (June 2023), and also included Parkinson's disease. Due to a reorganisation, the assignment was given to NOMA (December 2023).

In a single technology assessment, the technology (a pharmaceutical or a device) is appraised based on documentation submitted by the company owning the technology, or their representatives ("the submitter"). The submitter in this assessment is Insightec, the company owning *ExAblate Neuro system*.

In initial meetings, the submitter claimed that the evidence for Parkinson's disease was insufficient and asked to submit documentation only for essential tremor. The assignment was therefore changed to only involve essential tremor (March 2024). NOMA received the first documentation from the submitter 29.04.2024. This documentation had several shortcomings, and after a few meetings and communications, the submitter revised the documentation. NOMA received the revised documentation 17.07.2024. A progress log that details the communication and progress is provided in Appendix 1.

Contributors

Internal team members at NOMA:

- Jon-Vidar Gaustad, project manager and responsible for effect and safety
- Ida-Kristin Ørjasæter Elvsaas, effect and safety
- Anna Lien Espeland, health economics (responsible)
- Gunn Eva Næss, literature search/information retrieval (responsible)
- Anna Stoinska-Schneider, contact person and internal reviewer

External experts (recruited by "Nye metoder"):

- Espen Dietrichs, Senior physician and professor, Oslo University Hospital, Department of Neurology
- Sasha Gulati, Senior physician and professor, St. Olav's Hospital, Department of Neurosurgery
- Silje Bjerknes, Senior physician, Oslo University Hospital, Department of Neurology

Patient representative:

- Silje Bergerud, Chair of the ET patient association "*Essensiell Tremor-Foreningen Norge*"

We thank Geir Smedslund, and Elisabet Hafstad for internal review and comments to the report. We also thank Anna Stoinska-Schneider for support and review of the report.

Conflicts of interest

The external experts and patient representative have completed a conflict-of-interest form, and no conflicts of interest have been reported.

NOMA is solely responsible for the content of this report.

Martin Lerner	Jon-Vidar Gaustad
Head of Unit	*Project Manager*

List of abbreviations

AE, adverse event

BIA, budget impact analysis

DBS, Deep Brain Stimulation

CRST, Clinical Rating Scale for Tremor

ET, Essential Tremor

EQ-5D, EuroQol Five Dimension (standardised tool for measuring health-related quality of life, created by the EuroQol Group)

FTM, Fahn-Tolosa-Marin Rating Scale

HSUV, health state utility value

HTA, Health Technology Assessment

ICER, incremental cost-effectiveness ratio

MRgFUS, Magnetic Resonance-guided Focused Ultrasound

MRI, magnetic resonance imaging

NMB, net monetary benefit

NOK, Norwegian krone

NOMA, Norwegian Medical Products Agency

QALY, quality-adjusted life-year

QUEST, Quality of Life in Essential Tremor

STA, Single Technology Assessment

TETRAS, Tremor Research Group Essential Tremor Rating Scale

VAT, value added tax

WTP, willingness-to-pay

1. Background

1.1 Essential tremor

1.1.1 Description of the disease

Essential tremor (ET) is a neurological disorder characterised by involuntary rhythmic shaking of one or more body parts, not caused by other known conditions (1). An important part of diagnosis is therefore to rule out other possible causes of tremor such as Parkinson's disease, ataxia, dystonia, or medication-induced tremor. The most common symptom of ET is shaking of hands, but shaking of head, voice, or other body parts may also occur (2;3). The tremors can disappear at rest, but typically appear during activity or when a posture is maintained (2). The symptoms are often worsened by caffeine, excitement, anxiety, stress, or exhaustion, and may be reduced by alcohol (4). The severity of ET varies substantially between individuals. Some experience mild tremors that only cause minor impact on daily activities, while others have severe tremors that impair daily activities and substantially reduce quality of life (2;3).

1.1.2 Prevalence and etiology

ET is one of the most common neurological disorders. An exact determination of the prevalence is difficult because some patients are not diagnosed, and others are misdiagnosed (5). In a recent meta-analysis, Song and colleagues reported a prevalence of 0.32% in the global population and showed that that prevalence increases with age (6). The prevalence was also found to be higher for men than women (6). In another meta-analysis, Louis and Ferreira found a prevalence of 0.9% for all ages, and a prevalence of 4.6% for those 65 years and older (7). Although the two meta-analyses reported different absolute values for overall prevalence, the analyses agreed that the prevalence increases markedly with age. Our clinical experts argued that the higher prevalence is more in line with their experience than the lower prevalence.

Symptoms of ET usually appear in adulthood, typically after the age of 40, but may also appear during childhood. Once presented, ET is a chronic disorder that usually progresses with time (2). The causes of ET are not fully understood but probably involves both genetic and environmental factors. The prevalence of ET is enhanced in some families. Mutations in specific genes have been suggested to play a role, but few genetic causes of ET are known (8). The ET symptoms are believed to be caused by dysfunction within the cerebellum and its connectors, and the ventral intermediate nucleus of the thalamus has been the target area for surgical treatment of tremors (3;9-11). More recently, the posterior hypothalamic area has been introduced as an alternative and possibly even better target (12).

1.1.3 Current treatment options

There is currently no cure for ET. The purpose of the treatments is thus to reduce the severity of the symptoms. First-line treatment for patients with moderate to severe ET involves pharmaceutical interventions, such as the beta-blocker propranolol (originally intended for heart conditions), or epilepsy drugs such as primidone and topiramate (3). Pharmaceutical treatment is often combined with guidance on exercise, physical activity, nutrition and lifestyle. The pharmaceutical treatments reduce tremor severity in many patients, but about half the ET patients experience unsatisfactory response and/or substantial adverse effects (13). Patients who do not respond satisfactorily to pharmaceutical treatment can be offered deep brain stimulation (DBS). DBS involves surgical implantation of electrodes deep within the brain. The electrodes provide electrical stimulation to specific regions of the brain and can reduce tremors. In Norway, DBS is offered at Oslo University

Hospital and St. Olavs Hospital (4). Only a small number of ET patients are eligible for DBS or willing to undergo the surgical procedure. Norwegian doctors estimate that 20–30 ET patients undergo DBS surgery each year in Norway. New treatment options are needed for patients with moderate to severe ET that do not respond satisfactorily to medication, and are ineligible or unwilling to undergo DBS.

1.2 MRgFUS

Magnetic Resonance-guided Focused Ultrasound (MRgFUS) is used to create a permanent lesion in the part of thalamus that is involved in causing tremor symptoms. The lesion is created by thermal heating induced by high-intensity focused ultrasound, and the treatment is monitored by MR imaging. Insightec's *ExAblate Neuro system* uses a 1024-element phased array transducer to deliver the ultrasound energy. According to Insightec, the ultrasound energy can be delivered with submillimeter precision and normal tissue only 0.2 millimeter from the target area can be preserved. The *ExAblate Neuro system* received CE-marking in 2012 which indicate that the MRgFUS device meets the EU safety, health, and environmental protection requirements. MRgFUS is available in several European countries, including Germany, Denmark, Spain, Finland, Austria, Poland, Portugal, Italy, Greece, France, Switzerland, the United Kingdom, and Sweden.

1.2.1 Planning and preparation

Before MRgFUS, a CT scan is required to assess skull properties including the skull density. The skull properties influence transmission of ultrasound energy through the skull and are considered when the targeting strategy is planned. MR scans may also be acquired for planning the treatment target area. Shortly before MRgFUS, the patient's head is shaved, and a stereotactic frame is placed under local anesthesia. The frame ensures that the head will be completely still during the treatment in which the patient will be awake.

1.2.2 MRgFUS treatment

During MRgFUS treatment the patient is placed within a MR scanner and imaging is used to monitor the treatment. The treatment procedure consists of four steps:

1. Anatomical MR images are obtained of the patient in the "treatment position". These images are considered together with the CT and MR scans that were recorded during planning, and the planned targeting strategy may be adjusted.
2. Low power ultrasound is applied, and MR thermography is used to confirm that the ultrasound energy is delivered to the target area. At this stage, the temperature is increased to 45°C and clinical symptoms are not expected.
3. Low power ultrasound is applied to create a transient effect. At this stage the temperature is increased to around 50°C and the awake patient is examined for changes in hand tremor symptoms and questioned for any unwanted effects such as numbness or pain. If needed, the target area can be adjusted.
4. After all adjustments have been made and confirmed, the ultrasound power is gradually increased while the temperature is monitored. The therapeutic ultrasound sonications typically last 10 to 25 seconds and are intended to increase the temperature to 58–60°C in the target area. These sonications produce the permanent lesions that are supposed to reduce tremor symptoms immediately.

The treatment procedure (step 1–4) inside the MR scanner lasts 3–4 hours, and approximately one hour is needed for the preparation (head-shave and stereotactic frame attachment). The procedure does not include surgery and is performed with the patient fully awake (no general anesthesia). Usually, patients do not need to stay more than two nights in the hospital.

One side of the brain is targeted during the procedure. This is referred to as unilateral MRgFUS and is intended to reduce tremor in the contralateral side of the patient. Patients with severe tremors in both sides of the body may be offered a second treatment session later. This is referred to as bilateral MRgFUS and is intended to reduce tremor in both sides of the patient body.

1.2.3 Number of ET patients expected to use MRgFUS in Norway

As described above, the meta-analysis by Song and colleagues reported an ET prevalence of 0.32% in the global population (6). This indicates that the number of persons with ET in Norway is 17 462 (considering a Norwegian population of 5.475 million). Song and colleagues also found that the prevalence of ET increases with age (6). By considering the age-specific prevalences and the number of persons within these age categories (as reported by Statistics Norway - SSB), the submitter estimated that the number of persons with ET in Norway was 27 343 (in 2022). The higher number reflects that the Norwegian population is older and thus have a higher prevalence of ET than the global population. It has been reported that 20% of ET patients seek medical care (14), that 30% of these are diagnosed with moderate or severe ET (15), and that 50% of patients with moderate to severe ET are refractory to pharmaceutical treatments (13). Taken together one can estimate that 820 persons have moderate to severe medication-refractory ET in Norway (27 343 * 0.20 * 0.30 * 0.50 = 820). Among these, 85% are assumed to be eligible for DBS (15). The submitter argues that patients who are ineligible to DBS or unwilling to undergo DBS are expected to use MRgFUS. According to the submitter, 100 patients per year is a conservative estimate of the number of ET patients that will use MRgFUS in Norway. The submitter has assumed that 30 ET patients will use MRgFUS the first year after implementation and that the number of ET patients will increase gradually to 100 five years after implantation, in their budget impact analysis.

Our clinical experts argued that more than 100 ET patients could undergo MRgFUS the first years after implementation (if the capacity is sufficient), because many ET patients are waiting for treatment. Furthermore, our clinical experts indicated that approximately 50 ET patients would undergo MRgFUS yearly, in the long run. Among these, our experts expected that approximately 30% will need two procedures (bilateral MRgFUS), resulting in 65 procedures per year.

NOMA realises that the number of relevant ET patients and the number of yearly MRgFUS procedures are somewhat uncertain. We have used the assumptions of our clinical experts in our analysis, but we underline that these assumptions do not differ substantially from the assumptions made by Insightec.

1.3 Objective and research question

The objective of the current STA was to investigate the clinical effect and safety of unilateral MRgFUS for patients with medication-refractory, moderate to severe ET who are ineligible or unwilling to undergo DBS. Additionally, to investigate the cost-effectiveness and budget impacts of implementing MRgFUS in Norway. Unilateral MRgFUS was compared to no procedure.

The clinical effectiveness and safety, as well as the cost effectiveness and budget impact analysis were appraised based on documentation submitted by Insightec.

2. Literature search

2.1 Inclusion criteria

The submitter presented a detailed list of inclusion criteria. Below is an overview of the essential inclusion criteria as interpreted by NOMA.

Population	Adult patients with moderate to severe essential tremors that do not respond adequately to medications
Intervention	Unilateral Magnetic Resonance-guided Focused Ultrasound (Unilateral MRgFUS) *
Comparator	Sham procedure, standard care, or no comparator
Outcome	1. Tremor severity, assessed by validated clinical rating scores 2. Quality of life, assessed by validated clinical rating scores 3. Adverse events
Study design	1. Systematic reviews 2. Randomised controlled trials (RCT) 3. Non-randomised studies (including controlled studies, cohort studies, before-and-after studies, cost effectiveness/minimisation studies)
Publication year	No limitation
Country	No limitation
Language	Article or abstract available in English

* Studies of bilateral MRgFUS were considered if they reported results from the first procedure (unilateral)

The following types of publications were excluded:

- Conference abstracts, editorials, articles in press, and case reports
- Studies with a sample size of less than 10 patients (regardless of study design)
- Prospective non-randomised before-and-after studies of less than 30 patients
- Retrospective non-randomised before-and-after studies of less than 100 patients

2.2 Literature search and selection of studies

The submitter performed a systematic literature search where terms for the population and intervention were combined using the Boolean search operator AND. Several relevant MeSH-terms and keywords were used, and search components such as truncation, quotation marks and parenthesis were used appropriately. The submitter searched the following databases in June 2024: Medline and Medline In-Process (U.S. National Library of Medicine), Embase (Ovid), Cochrane Central Register of Controlled Trials, U.S. National Library of Medicine Clinical Trials (clinicaltrials.gov) and WHO International Clinical Trials Registry Platform. The search strings for all databases are shown in full in Appendix 2.

The submitter identified 1964 unique references in the database searches (Figure 1). 1861 references were excluded after considering titles and abstracts, and 77 references were excluded after full-text review. The reasons for exclusion after full-text review were wrong population, intervention, comparison or study design for 26 references (Figure 1). The submitter also excluded 10 references that were conference abstracts, letters to the editor or systematic reviews that were substantially older than the systematic reviews that were included. Finally, 45 studies were excluded because they included fewer patients than required by the inclusion criteria (described above).

The submitter included 26 references: one RCT (described in 6 articles), 9 prospective non-randomised studies, 4 retrospective non-randomised studies (described in 5 articles), 2 systematic reviews and 4 health economic evaluations. The RCT and the non-randomised studies are described in detail below (Table 1 and Table 2). The systematic reviews were found to have critically low quality and were not used (described in *Chapter 3.2*

Methodological quality). The health economic evaluations are described in *Chapter 4 Health economic assessment*. Additionally, the submitter identified 6 ongoing studies. The ongoing studies are singe-arm studies (no comparator) and are listed in Appendix 4.

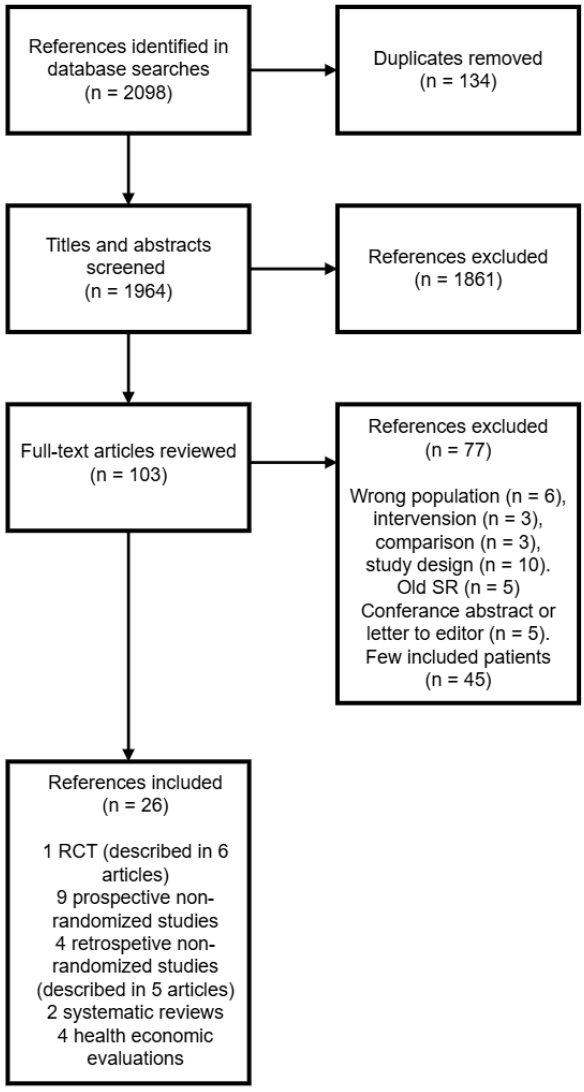

Figure 1. *PRISMA flow diagram illustrating selection of studies.*

2.3 NOMA's additional literature search and comments

NOMA performed additional searches in US National Library of Medicine Clinical Trials (clinicaltrials.gov) and WHO International Clinical Trials Registry Platform (ICTRP) in September 2024. The purpose of NOMA's searches was to investigate whether additional studies could be identified by using more comprehensive search strings. The full search strings of NOMA's searches are shown in Appendix 3. NOMA's searches did not identify additional studies that fulfilled the inclusion criteria.

NOMA identified three health technology assessments (HTAs) that evaluated MRgFUS for essential tremor. The HTAs were conducted by the Austrian Institute for Health Technology Assessment in 2023 (16), HTA Syd in Sweden in 2023 (17), and by Health Quality Ontario in Canada in 2018 (15). NOMA searched the lists of included studies in the HTAs but did not identify additional studies that fulfilled our inclusion criteria.

NOMA deems that it is likely that all relevant studies have been identified and included.

3. Evaluation of clinical effectiveness

3.1 Description of included studies

3.1.1 Description of the included RCT

The submitter included one RCT (Elias 2016; Table 1). Elias 2016 was a multicenter RCT conducted in USA, Canada, South Korea, and Japan. The study included 76 patients with moderate to severe essential tremor that had not responded to at least two trials of medical therapy (medication-refractory). The mean age of the patients was 71 years, the mean duration of the disease was 17 years, and the proportion of men was 68%. 56 patients were randomised to unilateral MRgFUS and 20 were randomised to sham. Patients that were randomised to sham were placed inside the MR-scanner with the stereotactic frame attached to their head as if they were supposed to get MRgFUS treatment. Only the treatment team were aware of the assignment. Both patients and evaluators were unaware of the treatment given (blinded) the first three months after treatment. After three months, patients that were given sham were offered MRgFUS (cross-over) and all patients were made aware of the treatment (unblinded). The RCT was first described in a publication by Elias and coworkers who reported outcomes assessed in the first phase (the randomised, controlled, and blinded phase) (18). The unblinded extension phase (without control group) was later described in three publications with two to five years follow-up (19-21). Additionally, one publication has described secondary analyses of the patients included in the RCT (22), and another has described patients that were treated at one of the RCT-institutions within the same time period (23). The latter publication may report the same patients as the RCT, and the results from this publication are not reported separately in our report (to avoid double-counting of patients). The RCT reported hand tremor score assessed by Clinical Rating Scale for Tremor (CRST) part A and B, disability score assessed by CRST part C, quality of life assessed by Quality of Life in Essential Tremor (QUEST) questionnaire, and adverse events (Table 1).

Table 1. *Description of the included RCT*

Study (reference), design, country	Diagnosis, age, disease duration, gender *	Intervention and comparator	Outcome and follow-up
Elias 2016 (18-23) RCT USA, Canada, South Korea, Japan	Moderate to severe medication-refractory ET, age: 71±8 y, duration: 17±12 y, male: 68%	MRgFUS (n=56) Sham (n=20)	CRST A+B, CRST C, QUEST, AE RCT-phase: 3 m follow-up Non-RCT-phase: 60m follow-up

***** Age and ET duration is reported as mean ± standard deviation. **Abbreviations:** AE, adverse events; CRST, Clinical Rating Scale for Tremor (A+B and C indicate parts of the test); ET, essential tremor; m, months; n, number of patients; QUEST, Quality of Life in Essential Tremor; y, years

3.1.2 Description of the included non-randomised studies

Thirteen non-randomised studies were included (nine prospective and four retrospective studies with a before-and-after design). The non-randomised studies were conducted in USA, Japan, Spain, Italy, China, Australia, Germany, and Israel (Table 2). The studies included patients with medication-refractory ET that were characterised as moderate to severe, severe, or disabling ET. The mean or median age of the patients varied from 62 to 75 years and the proportion of men varied from 61% to 80%. The average disease duration varied from 13 to 30 years, and the number of patients varied from 30 to 215. Together the studies reported a range of outcomes. Hand tremor scores, disability scores and quality of life were assessed by different scales as detailed in Table 2. The studies reported baseline

scores and compared these with scores assessed at various times after unilateral MRgFUS. Most of the studies also reported adverse events.

Table 2. *Description of the included non-randomised studies (13 studies)*

Study (reference), design, country	Diagnosis, age, disease duration, gender *	Intervention and comparator	Outcome and follow-up
Abe 2021 (24), Prospective B-A, Japan	Moderate to severe medication-refractory ET, age: 71±9 y, ET duration: 24±17 y, male: 77%	MRgFUS (n=35) No control group	CRST A+B, CRST C, QUEST, AE 12 m follow-up
Arcadi 2024 (25), Prospective B-A, Spain	Disabling medication-refractory ET, age: 73±9 y, ET duration: 26±17 y, male: 68%	MRgFUS (n=127) No control group	CRST A+B, CRST C, AE 6 m follow-up
Gasca-Salas 2019 (26), Prospective B-A, Spain	Disabling medication-refractory ET, age: 64±14 y, ET duration: 17±11 y, male: 74%	MRgFUS (n=36) No control group	FTM, neurological examination 12 m follow-up
Golfrè Andreasi 2024 (27), Prospect-ive B-A, Italy	Disabling med.-refractory ET, age: 73 [67,76] y, ET duration: 26 [17,55] y, male: 80%	MRgFUS (n=35) No control group	TETRAS, AE 12 m follow-up
Lu 2022 (28), Prospective B-A, China	Severe medication-refractory ET, age: 62±11 y, ET duration: 18±10 y, male: 70%	MRgFUS (n=35) Healthy (no ET) controls (n=30)	CRST A+B, CRST C 6 m follow-up
Peters 2024 (29), Prospective B-A, Australia	Severe medication-refractory ET, age: 62±11 y, ET duration: 30±17 y, male: 77%	MRgFUS (n=30) No control group	CRST A+B, QUEST, AE 36 m follow-up
Purrer 2022 (30), Prospective B-A, Germany	Severe medication-refractory ET, age: 75±8 y, ET duration: 30±16 y, male: 68%	MRgFUS (n=45) No control group	CRST A+B, CRST C, QUEST, SF-36, AE 12 m follow-up
Sinai 2019 (31), Prospective B-A, Israel	Disabling medication-refractory ET, age: 71(63-87) y, ET duration: 16±10 y, male: 61%	MRgFUS (n=44) No control group	CRST hand, QUEST, AE 60 m follow-up
Zur 2020 (32), Prospective B-A, Israel	Disabling medication-refractory ET, age: 72±6 y, ET duration: 13±8 y, male: 64%	MRgFUS (n=37) No control group	CRST hand, QUEST 6 m follow-up
Blitz 2023 (33), Retrospective B-A, USA	Severe or disabling medication-refractory ET, age: 75±7 y, male: 71%	MRgFUS (n=215) No control group	FTM, AE 12 m follow-up
Hino 2024 (34), Retrospective B-A, Japan	Moderate to severe medication-refractory ET, age: 70±12 y, ET duration: 27±18 y, male: 73%	MRgFUS (n=101) No control group	CRST A+B, CRST C, AE 3 m follow-up
Lak 2022 (35;36), Retrospective B-A, USA	Medication-refractory ET, age: 75±8 y, ET duration: 28±18 y male: 68%	MRgFUS (n=150) No control group	CRST A, AE 24 m follow-up
Mueller 2024 (37), Retrospective B-A, USA	Severe medication-refractory ET, age: 73±9 y, ET duration: 21±16 y male: 66%	MRgFUS (n=139) No control group	CRST B, AE 3 m follow-up

***** Age and ET duration is reported as mean ± standard deviation, median [interquartile range], or median (range)

Abbreviations: AE, adverse events; B-A, before-and-after study; CRST, Clinical Rating Scale for Tremor (A+B and C indicate parts of the test); ET, essential tremor; m, months; FTM, Fahn-Tolosa-Marin Rating Scale; m, months; n, number of patients; QUEST, Quality of Life in Essential Tremor Questionnaire; SF-36, short form health survey; TETRAS, Tremor Research Group Essential Tremor Rating Scale; y, years

3.2 Methodological quality

3.2.1 Risk of bias in the included RCT

The submitter evaluated risk of bias in the included RCT by using Cochrane risk of bias 1 (38), and assessed risk of bias on a study level rather than for individual effect estimates. Elias 2016 is a randomised double-blinded study, but after three months patients that received sham were offered MRgFUS (cross-over) and made aware of the treatment (unblinded). Therefore, different assessments were needed for effect estimates obtained within the first three months than for estimates obtained in the unblinded (non-randomised) study extension. NOMA assessed risk of bias using Cochrane risk of bias 2 (39), and assessed risk of bias for individual effect estimates. Here we present NOMA's assessment of risk of bias which was performed by two researchers.

The risk of bias was low in all domains for hand tremor scores assessed one and three months after treatment (Figure 2). The risk of bias was also low for disability score and quality of life assessed three months after treatment (Figure 2). After three months, the study was no longer randomised or blinded, and the effect estimates had high risk of bias (as the non-randomised studies described below). Elias 2016 was partly funded by Insightec (the company owning the MRgFUS device *ExAblate Neuro system*).

		Domain 1–5: Risk of bias due to:					Overall risk of bias
Study	**Outcome considered**	Randomisation process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	
Elias 2016	Hand tremor score (CRST A+B), 1 and 3 months						
Elias 2016	Disability score (CRST C), 3 months						
Elias 2016	Quality of life (QUEST), 3 months						

Figure 2. *Risk of bias in the included RCT. Green indicates low risk. None of the effect estimates obtained at one and three months were deemed to have 'some concerns' or 'high risk'. This would have been indicated with yellow and red color respectively. Abbreviations: CRST, Clinical Rating Scale for Tremor (A+B and C indicate parts of the test); QUEST, Quality of Life in Essential Tremor Questionnaire.*

3.2.2 Risk of bias in the included non-randomised studies

The submitter evaluated risk of bias in the included non-randomised studies by using the Joanna Briggs Institute Checklist for Quasi-Experimental Studies (40). The checklist consists of nine questions, and these have been answered appropriately by the submitter (all checklist answers are shown in Appendix 5). Most of the studies provided adequate details on the intervention and the outcomes, and measured outcomes in a reliable way. However, all the studies had a before-and-after design without control group. NOMA deems that this study design inherently causes high risk of bias. Additionally, some of the studies did not

provide sufficient details on the completeness of follow-up and the reasons for drop-out. In several studies, the number of patients was substantially lower at late time points than at early, which further adds risk of bias to effect estimates measured at late time points. Abe 2021 was funded by Insightec (the company owning the MRgFUS device *ExAblate Neuro system*). The other non-randomised studies were funded by non-profit organisations (such as national research institutions) or did not specify funding sources.

3.2.3 Methodological quality in the included systematic reviews

The submitter evaluated the methodological quality of the included systematic reviews by using the AMSTAR 2 checklist (41). The checklist consists of 16 questions in which 7 questions are defined as critical. All checklist answers are shown in Appendix 5. The two included systematic reviews had critically low quality and were not used in the current report.

3.3 Does MRgFUS reduce hand tremor?

3.3.1 Hand tremor score in the included RCT

Hand tremor score was the primary outcome in the RCT Elias 2016. Hand tremor score was reduced in the group that received MRgFUS but not in the group that received sham (Figure 3).

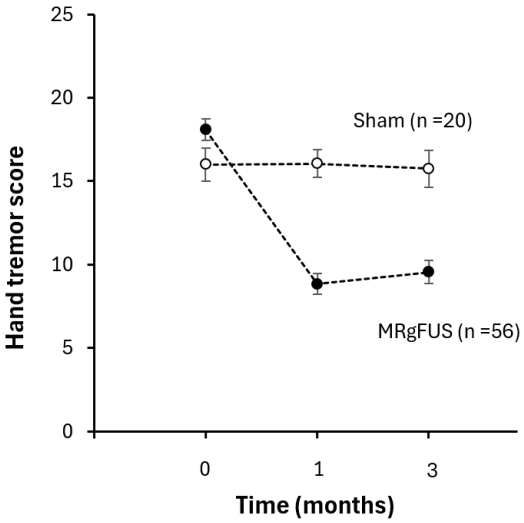

Figure 3. *Hand tremor score in ET patients subjected to MRgFUS (closed circles) or sham (open circles). Points show mean values, bars show ± standard error, and n refers to number of patients. Hand tremor score was assessed by Clinical Rating Scale for Tremor part A and B, a scale ranging from 0 to 32 where higher scores indicate more severe tremor.*

NOMA calculated effect estimates (i.e. mean difference; MD) for hand tremor scores assessed 1 and 3 months after the treatment. A forest plot displaying MD is shown in Figure 4. The patients that received MRgFUS showed lower hand tremor scores than the patients who received sham, at both time points (1 month: MD -7.21, 95% CI -9.23, -5.19; 3 months: MD -6.20, 95% CI -8.72, -3.68; Figure 4).

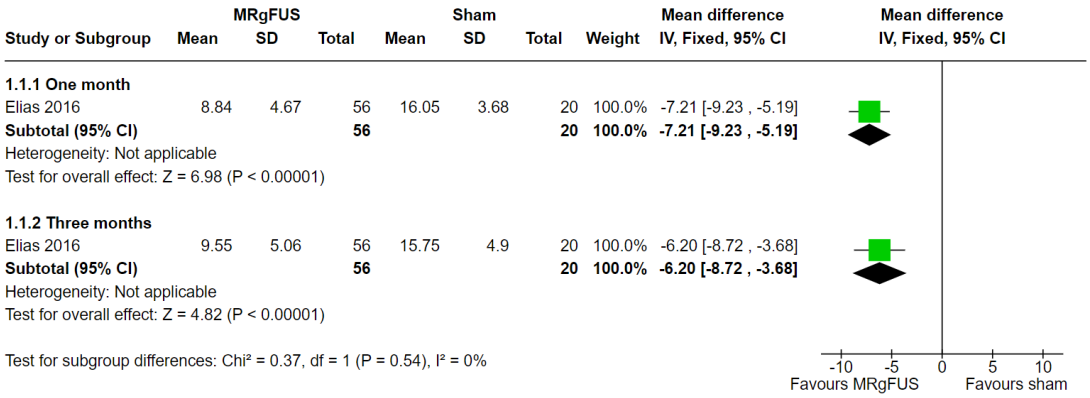

Figure 4. *Hand tremor score 1 and 3 months after MRgFUS or sham in patients with essential tremor. The effect estimates were calculated using using RevMan Web (42). Hand tremor score was assessed by Clinical Rating Scale for Tremor part A and B, a scale ranging from 0 to 32 where higher scores indicate more severe tremor.*

It is worth to mention that the effect of MRgFUS varied among individual patients. This is illustrated in Figure 5 which shows the reduction in hand tremor for the 56 patients that received MRgFUS. The average reduction in hand tremor was 47%. Twenty-seven patients (48%) experienced more than 50% reduction in hand tremor, 24 patients (43%) experienced 10–50% reduction, and 5 patients (9%) experienced less than 10% reduction in hand tremor (Figure 5).

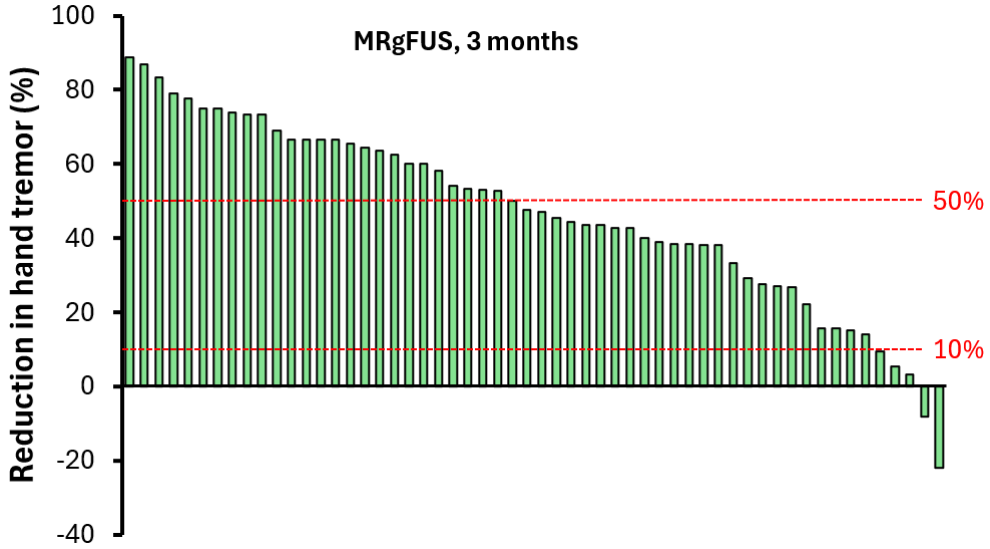

Figure 5.*. Reduction in hand tremor (i.e., % change between pre- and post-treatment score) in ET patients three months after MRgFUS. Columns show individual patients (n = 56). Red dashed lines highlight 10 and 50% reduction in hand tremor.*

After three months, patients that received sham were offered MRgFUS. In this extended study period, there was no control group. Post treatment hand tremor scores were lower than baseline scores for all time points in the five-year follow-up period, indicating sustained treatment effect (Figure 6). The authors noticed a trend towards increased hand tremor scores at the latest time points. This may imply that the treatment effect is reduced with time, but the authors also suggested that the increase in hand tremor scores may be due to higher patient age and progression of the disease (21). It should be noticed that the number of patients was substantially lower at the late time points. The authors specified that only a few of the patients that dropped out chose alternative procedures such as DBS (n = 6), whereas the majority were unwilling to return (n = 18), missed observation (n = 14), had an unrelated new medical condition (n = 7) or lost contact (n = 3). Nevertheless, the high proportion of patients that dropped out introduce risk of bias.

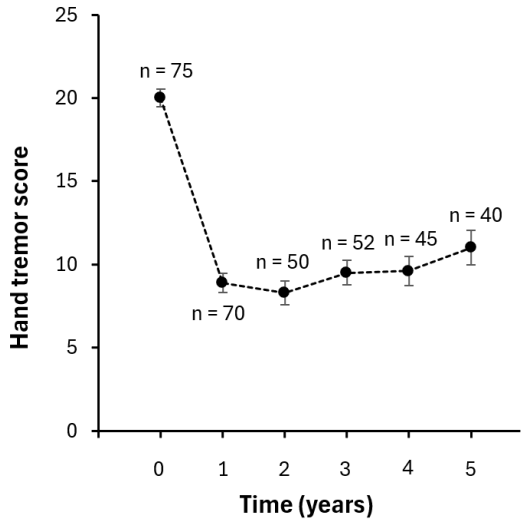

Figure 6. *Hand tremor scores at baseline (time = 0) and 1–5 years after MRgFUS treatment. Points show mean values, bars show ± standard error, n refers to number of patients. Hand tremor score was assessed by Clinical Rating Scale for Tremor part A and B, a scale ranging from 0 to 32 where higher scores indicate more severe tremor.*

3.3.2 Hand tremor score in non-randomised studies

The submitter also included non-randomised before-and-after studies reporting hand tremor scores. These studies used different tests/scales to assess hand tremor as described in Table 2. The studies also reported reduction in hand tremor (i.e., % change between pre- and post-treatment score). NOMA calculated weighted averages of the reductions in hand tremor. The average reduction was 60–70% the first two years and tended to be smaller at later time points (Figure 7). It should be noticed that the number of patients at late time points was substantially reduced because of drop-out, and because only a few studies reported hand tremor scores after more than 12 months. Reduction in hand tremor as well as number of patients in the individual studies are shown in Appendix 6.

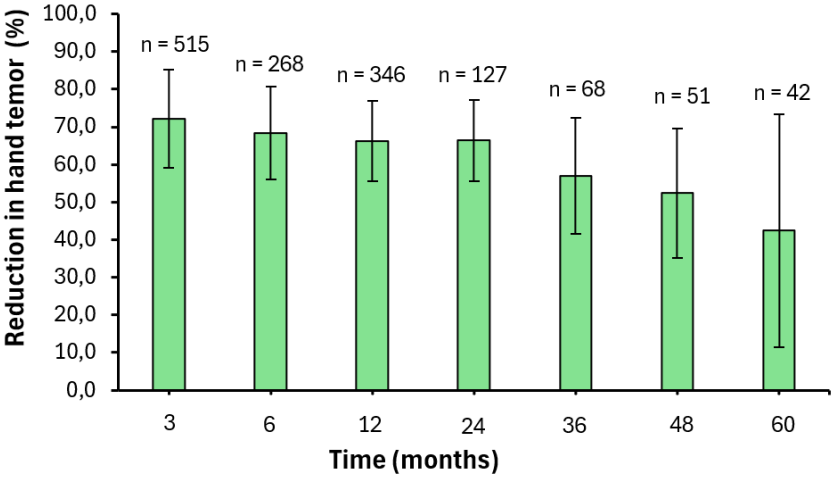

Figure 7. *Reduction in hand tremor at various time points after MRgFUS treatment (% reduction as compared to baseline score). Columns show weighted averages, bars show between-study standard deviations, and n refers to the total number of patients. Weighting was based on the number of patients in the individual studies.*

3.4 Does MRgFUS affect disability and quality of life?

3.4.1 Disability and quality of life in the included RCT

The RCT Elias 2016 also reported disability and quality of life (secondary outcomes). Disability was reduced and quality of life was improved in the group that received MRgFUS but not in the group that received sham (Figure 8).

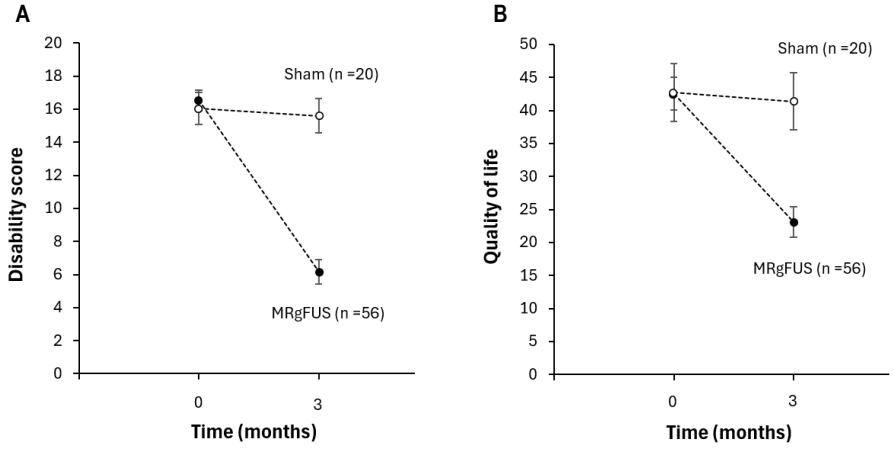

Figure 8. *Disability score (A) and quality of life (B) in ET patients subjected to MRgFUS (closed circles) or sham (open circles). Points show mean values, bars show ± standard error, and n refers to number of patients. Disability score was assessed by Clinical Rating Scale for Tremor part C, a scale ranging from 0 to 32 where higher scores indicate more severe disability. Quality of life was assessed by the Quality of Life in Essential Tremor (QUEST) questionary, where lower values indicate better quality of life.*

NOMA calculated effect estimates (i.e. mean difference; MD) for disability score and quality of life assessed 3 months after the treatment. Forest plots displaying MD are shown in Figure 9. The patients that received MRgFUS showed lower disability score and improved quality of life compared to patients who received sham (Disability score: MD -9.44, 95% CI -11.93, -6.95; Quality of life: MD -18.26, 95% CI -27.86, -8.66; Figure 9).

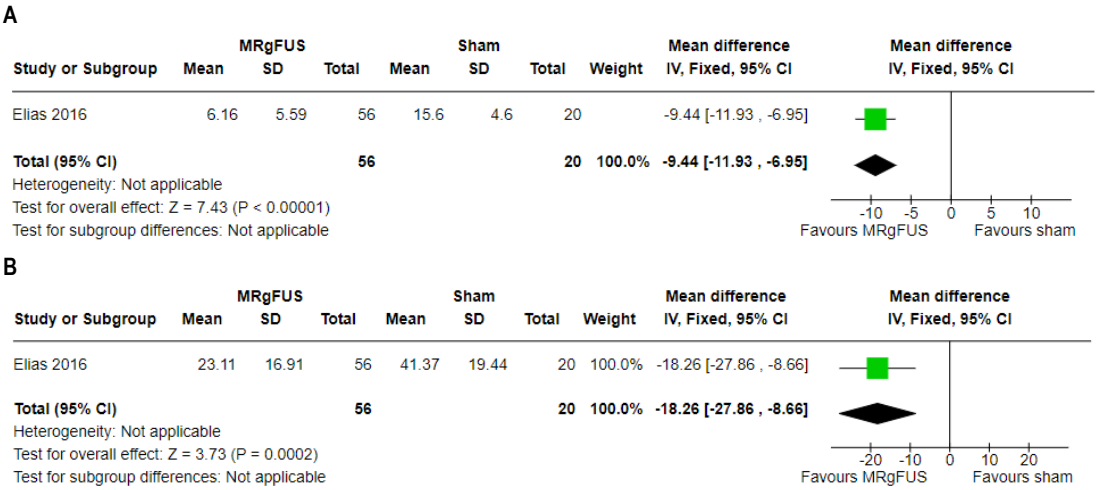

Figure 9. *Disability score (A) and quality of life (B) in ET patients 3 months after MRgFUS or sham. The effect estimates were calculated using using RevMan Web (42). Disability score was assessed by Clinical Rating Scale for Tremor part C, a scale ranging from 0 to 32 where higher scores indicate more severe disability. Quality of life was assessed by the Quality of Life in Essential Tremor (QUEST) questionary, where lower values indicate better quality of life.*

Disability score and quality of life were also assessed in the study extension phase (without control group). Post treatment scores were lower than baseline values for all time points in the five-year follow-up period, indicating sustained treatment effect (Figure 10). The authors

noticed a trend towards increased scores at later time points. This may imply that the treatment effect is reduced with time, but it should be noticed that the number of patients was substantially lower at the late time points.

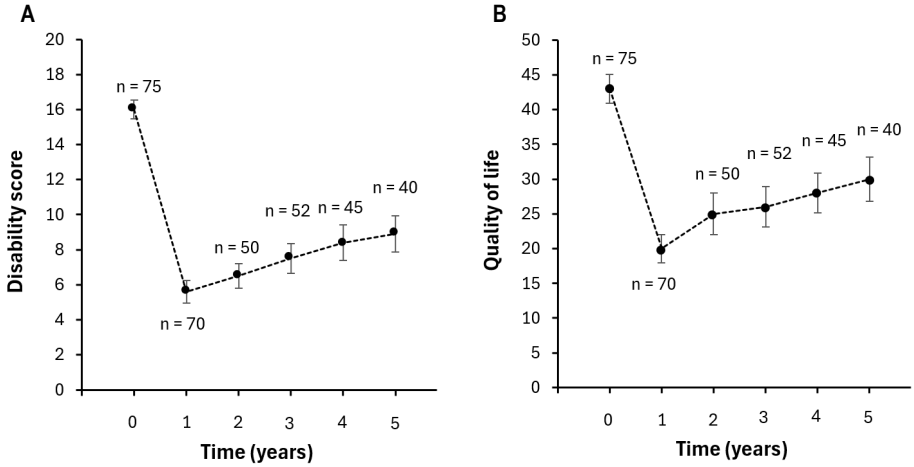

Figure 10. *Disability score (A) and quality of life (B) at baseline (time = 0) and 1-5 years after MRgFUS treatment. Points show mean values, bars show ± standard error, n refers to number of patients. Disability score was assessed by Clinical Rating Scale for Tremor part C, a scale ranging from 0 to 32 where higher scores indicate more severe disability. Quality of life was assessed by the Quality of Life in Essential Tremor (QUEST) questionary, where lower values indicate better quality of life.*

3.4.2 Disability and quality of life in non-randomised studies

Several of the included non-randomised studies reported changes in disability and quality of life (i.e., % change between pre- and post-treatment score). NOMA calculated weighted averages of the reduction in disability score and the improvement in quality of life. The average reduction in disability was 60–80% the first two years and tended to be smaller at later time points (Figure 11A). A similar trend was observed for quality of life (Figure 11B). It should be noticed that the number of patients at late time points was substantially reduced because of drop-out, and because only a few studies reported disability and quality of life after more than 12 months. Reduction in disability, improvement of quality of life, and the number of patients in the individual studies are presented in Appendix 6.

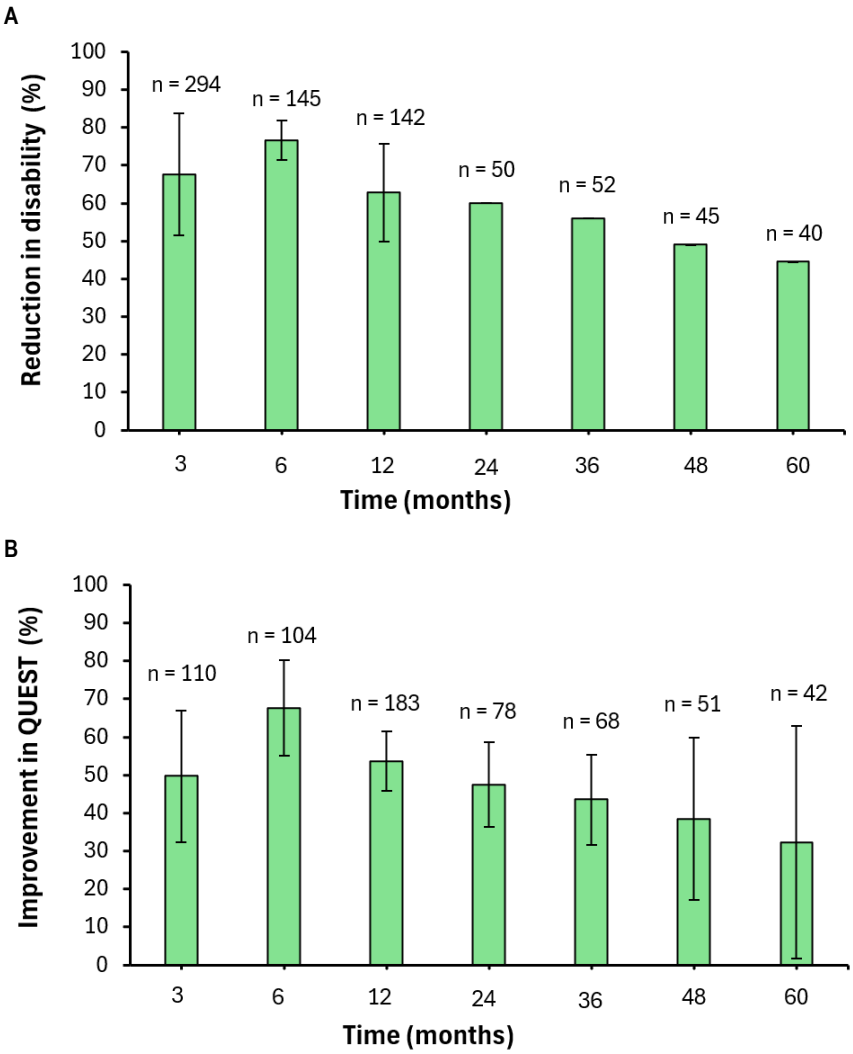

Figure 11. *Reduction in disability score (A) and improvement of quality of life (B) at various time points after MRgFUS treatment (% change between pre- and post-treatment score). Columns show weighted averages, bars show between-study standard deviations, and n refers to the total number of patients. Weighting was based on the number of patients in the individual studies. Disability score was assessed by Clinical Rating Scale for Tremor part C, a scale ranging from 0 to 32 where higher scores indicate more severe disability. Quality of life was assessed by the Quality of Life in Essential Tremor (QUEST) questionary, where lower values indicate better quality of life.*

3.5 Adverse events

3.5.1 Adverse events in the included RCT

The RCT Elias 2016 provided a detailed description of adverse events that occurred after unilateral MRgFUS or sham (Table 3). The most common adverse events were “paresthesia or numbness” and “gait disturbance”. These events occurred in 38% and 36% of the patients that underwent MRgFUS and in 5% of the patients that were given sham. Most of the adverse events resolved in time, but “paresthesia or numbness” and “gait disturbance” persisted in 14% and 9% of the patients 12 months after MRgFUS. New adverse events were not observed from the 12-month time point to the last follow-up at 5 years (21). The adverse events were generally characterised as mild or moderate, but one patient had dense and permanent hypesthesia of the dominant thumb and index finger which was categorised as a serious adverse event. In addition, one patient had a transient ischemic attack six weeks after MRgFUS. This was characterised as a serious adverse event but was deemed to be unrelated to MRgFUS (18).

Table 3. *Adverse events occurring after treatment*

Adverse event	MRgFUS (n = 56)				Sham * (n = 20)
	Total	1 d	3 m	12 m	
Paresthesia or numbness	21 (38%)	18 (32%)	14 (25%)	8 (14%)	1 (5%)
Gait disturbance	20 (36%)	19 (34%)	9 (16%)	5 (9%)	1 (5%)
Taste disturbance	3 (5%)	3 (5%)	2 (4%)	2 (4%)	0
Dysmetria, limb	7 (12%)	7 (12%)	5 (9%)	2 (4%)	0
Weakness, contralateral	2 (4%)	2 (4%)	2 (4%)	1 (2%)	0
Dysarthria	1 (2%)	1 (2%)	1 (2%)	0	0
Dysphagia	1 (2%)	1 (2%)	1 (2%)	0	0
Headache lasting >1 day	8 (14%)	8 (14%)	2 (4%)	0	4 (20%)
Fatigue	3 (5%)	3 (5%)	1 (2%)	0	1 (5%)
Disequilibrium sensation	5 (9%)	5 (9%)	3 (5%)	1 (2%)	0
Tinnitus	3 (5%)	3 (5%)	0	0	0
No adverse event	6 (11%)				8 (40%)

Abbreviations: d, day; m, month; n, number of patients
*, only one value was reported for sham patients in Elias 2016. We have interpreted that this refers to 'total'.

Elias 2016 also reported events that occurred during the procedure. The intraprocedural sensations and events were brief and typically resolved within seconds after the treatment ended. The most common intraprocedural events were "head discomfort", "vertigo", and "nausea" (Table 4), and these occurred more frequent among patients that received MRgFUS than among patients that received sham. Five MRgFUS treatments were interrupted because of pain, nausea, vertigo, or vomiting. A stereotactic frame was attached to the patient's head to ensure that the head was completely still during the treatment. 30-35% of the patients experienced pin-site pain, edema, or bruising that could be attributed to the placement of the stereotactic frame.

Table 4. *Adverse events occurring during the procedure*

Intraprocedural sensations or events	MRgFUS (n = 56)	Sham (n = 20)
Head discomfort: "heat" or "pressure"	17 (30%)	0
Vertigo: "dizzy"	12 (21%)	2 (10%)
Nausea	11 (20%)	0
Vomiting	2 (4%)	1 (5%)
Scalp tingling	4 (7%)	1 (5%)
Back pain	5 (9%)	1 (5%)
Anxiety	3 (5%)	2 (10%)

Abbreviations: n, number of patients

3.5.2 Adverse events in non-randomised studies

Ten of the included non-randomised studies reported adverse events (Table 2). The studies characterised the adverse events differently, but generally the adverse events were found to be common, mild and transient. The frequency of the adverse events did not differ substantially from the frequencies reported in the RCT Elias 2016 (described above). Except Golfrè Andreasi 2024 and Arcadi 2024, none of the non-randomised studies reported severe adverse events after MRgFUS. Golfrè Andreasi 2024 characterised a case of ataxic hemiparesis that persisted 12 months after MRgFUS as a severe adverse event (27), and in Arcadi 2024, five cases at the one-month follow-up were characterised as severe (two cases of limb weakness on the treated side, one of gait ataxia, one of dysmetria on the treated arm, and one of ataxia and dysarthria) (25). No severe adverse events were observed at the six-month follow up in the latter study.

3.6 NOMA's certainty in the evidence

NOMA used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (43) to assess the certainty of effect estimates measured at selected time points. The GRADE assessments are presented in Table 5.

Our certainty in the effect estimates measured three months after MRgFUS is high or moderate. These effect estimates are based on the RCT (Elias 2016) and are obtained within the randomised and blinded phase. The number of patients in the RCT was limited (n = 76), but NOMA's power analysis (with α =0.05 and β = 0.2) found that the statistical power was sufficient to detect relevant differences. Additionally, several non-randomised studies reported the same outcomes at the same time point, and all agreed with the RCT.

Our certainty in the effect estimates measured after three months is low or very low. These effect estimates are based on non-randomised before-and-after studies without control groups. Our certainty is reduced because this study design inherently causes high risk of bias.

The frequency of adverse events did not differ substantially between the RCT and the non-randomised studies, but NOMA generally rely more on the results that were reported in the RCT. It should be noted that the number of included patients was relatively small in all the included studies. It is thus possible that larger studies could have detected rare severe events (if such occur).

Table 5. *GRADE evidence profile*

Outcomes	Certainty assessment				Absolute or relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence
	Risk of bias	Inconsistency	Indirectness	Imprecision			
3 months							
Hand tremor	not serious	not serious	not serious	not serious	**MD -6.2** (-8.7, -3.7)	**76** (1 RCT)	⊕⊕⊕⊕ High
Disability	not serious	not serious	not serious	not serious	**MD -9.4** (-11.9, -7.0)	**76** (1 RCTs)	⊕⊕⊕⊕ High
Quality of life	not serious	not serious	not serious	serious[a]	**MD -18.3** (-27.9, -8.7)	**76** (1 RCT)	⊕⊕⊕◯ Moderate[a]
12 months							
Hand tremor	very serious[b]	not serious	not serious	not serious	**Red: 66.2%** (58.7, 73.6)	**346** (8 non-RCT)	⊕⊕◯◯ Low[b]
Disability	very serious[b]	not serious	not serious	not serious	**Red: 62.8%** (48.2, 77.3)	**142** (3 non-RCT)	⊕⊕◯◯ Low[b]
Quality of life	very serious[b]	not serious	not serious	not serious	**Impr: 53.7 %** (46.8, 60.6)	183 (5 non-RCT)	⊕⊕◯◯ Low[b]
36 months							
Hand tremor	very serious[b]	not serious	not serious	serious[c]	**Red: 57.1%** (39.6, 74.5)	68 (3 non-RCT)	⊕◯◯◯ Very low[b,c]
Disability	very serious[b]	not serious	not serious	serious[c]	**Red: 56.1%** (NA)	52 (1 non-RCT)	⊕◯◯◯ Very low[b,c]
Quality of life	very serious[b]	not serious	not serious	serious[c]	**Impr: 43.6 %** (30.1, 57.0)	68 (3 non-RCT)	⊕◯◯◯ Very low[b,c]

Our certainty in the evidence was downgraded because: **a,** the confidence interval was wide and included small and large effects; **b**, the included studies had high risk of bias; **c**, high number of missing patients (drop-outs).
Abbreviations: CI, confidence interval; Impr., improvement compared to baseline; NA, not applicable; Red., reduction compared to baseline

GRADE grades of evidence (43)

High certainty: we are very confident that the true effect lies close to that of the effect estimate.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

4. Organisational considerations

4.1 Locations for MRgFUS

As described in chapter 1.2.3, the submitter has suggested that 100 patients will undergo MRgFUS yearly. Because the procedure lasts 3–4 hours, two patients may be treated per day, per treatment center. The submitter has suggested that MRgFUS can be offered at two different locations in Norway. This organisation is similar to DBS which is currently offered at Oslo University Hospital and St. Olavs Hospital (4). Decision makers may also consider offering MRgFUS at one location. One location (instead of two) would half investment costs and the need for specially trained personnel.

4.2 Personnel and training

The MRgFUS procedure requires a team of personnel with different qualifications. According to the submitter, the team should include a neurologist, a neurosurgeon, a MR-technician/MR-physicist, and a nurse. The assumed time and costs for personnel are detailed in chapter 5 *Health economic assessment*. The submitter emphasised that the MRgFUS procedure requires skill acquisition. Training of the multidisciplinary team was not described, but the submitter indicated that 20 procedures were required for certification and that a learning curve of 50 procedures can be expected.

4.3 Need for MRI

Patients are placed within an MR-scanner during the MRgFUS procedure which lasts 3–4 hours. Additionally, MRI and CT-scans are performed before the procedure (to plan the treatment). Costs for MRI and CT have been included in the health economic evaluation. Decision makers should also consider how MRgFUS will influence the overall MR capacity. As described above, the submitter suggested that 100 patients will undergo MRgFUS yearly, and that two patients can be treated per day. This means that a MR-scanner must be allocated for MRgFUS 50 days per year (approximately one day per week).

5. Health economic assessment

5.1 Methods

Methods for evaluating submitted cost-effectiveness models

The basic aim of any economic evaluation is to identify, measure and compare costs and consequences of the alternatives under consideration. This is done in an incremental analysis in which the differences in costs between an intervention and its comparator, are compared with differences in consequences. Economic evaluations support decision making by informing the three criteria for priority setting in the Norwegian health care sector: 1) the benefit criterion, 2) the resource criterion, and 3) the severity criterion (44).

The primary objectives of health economic modelling are to provide a mechanism to determine the relative cost-effectiveness of the specified health intervention(s) compared to standard practice using the best available evidence, and to assess the most important sources of uncertainty surrounding the results. To make comparisons across different treatment or test strategies and multiple health outcomes, economic models typically measure health outcomes in terms of quality-adjusted life-years (QALYs). This is a variable designed to capture both life extension and health improvement. QALYs, by definition, take on a value of 1 for perfect health and 0 at death. The output of a cost-effectiveness model is expressed as an incremental cost-effectiveness ratio (ICER), which can be thought of as the extra cost of obtaining an extra life-year in perfect health. The ICER is defined as:

$$(Cost_{Intervention} - Cost_{Comparator}) \,/\, (QALY_{Intervention} - QALY_{Comparator})$$

There is no single correct way to build economic models estimating the cost-effectiveness of a specific health intervention. Modelling requires consulting with clinical experts to gain understanding of expected disease progression, and to determine the relevant treatment population, comparators, health outcomes and adverse events connected to treatment. This information informs the basic model structure and determines which clinical effect data are most important to retrieve in the systematic literature search. Once the model structure is in place, systematic searches and evidence grading are used to assess the model input parameters and relevant cost and quality of life data that is needed for cost-effectiveness calculations.

A model is rarely meant to capture every potential detail of the treatment landscape; rather the goal is to include sufficient details to provide a realistic view of the most significant pathways in disease progression, given the research question(s) one is trying to answer. Appraisal of health economic model is primarily about determining whether

- the choices made by the submitter regarding model structure and treatment comparator are reasonable
- baseline epidemiological data reflect the population in which the analysis is being performed
- the clinical effect data used in the model have adequate quality
- resource use and costs reflect the conditions of the healthcare system in question
- there has been sufficient sensitivity and scenario analyses to determine the degree and sources of uncertainty in the model results
- the model displays external and internal validity

The STA is based on a submitted model from the manufacturer. We have appraised the model and inputs, and made some revisions to the analyses.

5.1.1 Cost-effectiveness model provided by the submitter

The submitter has conducted a cost-utility analysis to evaluate the cost-effectiveness of unilateral MRgFUS for patients with medication-refractory, moderate to severe ET who are ineligible or unwilling to undergo DBS, compared to best supportive care in Norway (comparator "no procedure"). Utility is measured in QALYs. The model, constructed using Microsoft Excel, combines a decision tree and a Markov model. The Markov model should capture long-term costs and health outcomes. See key features of the model in Table 6.

Table 6. *Key features of the model copied from the submission*

Model element	Description
Time horizon	Time horizon for the decision tree: one year Time horizon for the long-term Markov: lifetime (40 years)
Cycle length	One year, with half cycle correction
Annual discount rate (costs and benefits)	4% p.a. (costs and benefits) for long-term component
Sensitivity analysis	Deterministic sensitivity analysis, probabilistic sensitivity analysis

The comparator groups are treated with best supportive care with medication (or no medication). Individuals in the intervention group go through MRgFUS alongside medication (or no medication). In the model, one can choose to include medication or not for either group. In the submitted main analysis, medication has been included for the MRgFUS group only.

The model starts with a decision tree for the first year. The decision tree is used to capture costs, utilities and treatment-related adverse events and mortality during the first year. Patients who are treated with MRgFUS have one of three outcomes based on the Clinical Rating Scale for Tremor (CRST): marked improvement; mild-to-moderate improvement or unsuccessful procedure. These were categorised based on level of tremor improvement in Fahn 1988 (45).

Text copied from the submission:
"The definitions of outcomes are:

- *Marked improvement in tremor: 50%-100% improvement compared with baseline.*
- *Mild-to-moderate improvement: 10%-50% improvement.*
- *Unsuccessful procedure: <10% improvement.*

A proportion of those who experience no improvement or worsening of tremor (i.e., have an unsuccessful procedure) will undergo reoperation.

Tremor recurrence which occurs shortly after surgery (< three months) can be the result of suboptimal lesion size or location (MRgFUS), …. The model assumes that the probability of an unsuccessful procedure will capture tremor recurrence that occurs within the first three months of surgery. This assumption was also made in Li et al.)" (46).

After year 1 the patients enter the Markov Model. The decision tree is presented in Figure 12, and Markov model in Figure 13.

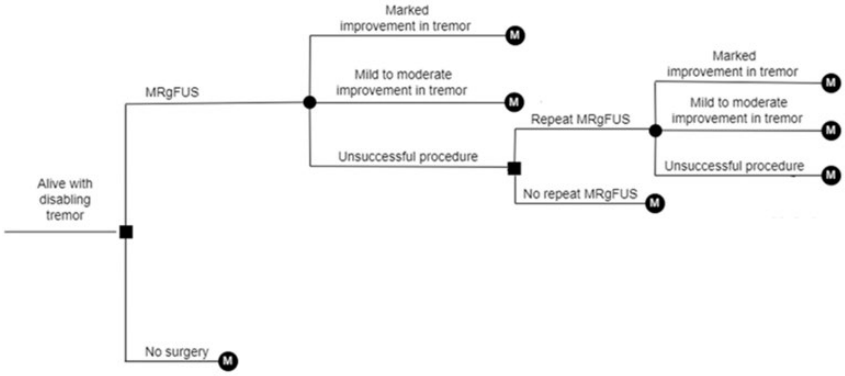

Figure 12. *Decision tree provided by the submitter*

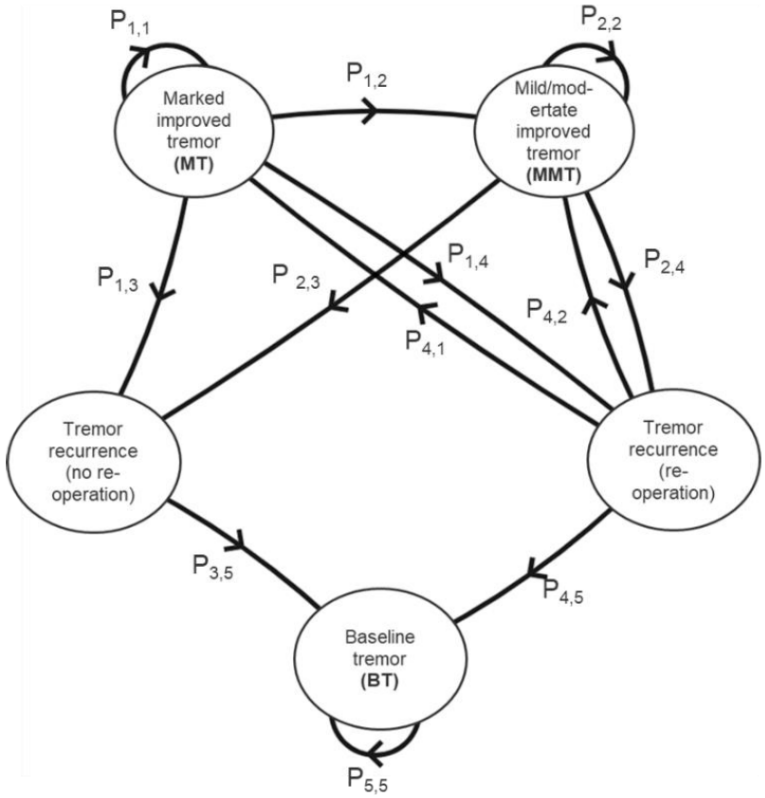

Figure 13. *Markov model provided by the submitter. The "P1,1" and "P1,2" etc. in the model are the transitions with transition probabilities.*

5.1.2 NOMA's comments on the model structure

The model could have been simplified, e.g. include fewer health states, yet still capture main differences in QALYs and costs. The model does seem to capture the main outcomes for the patient population. The model is also transparent and possible to edit.

According to the submitter the model has not been validated externally, but they state that it is basically the same which has been used in Jameel 2022 (47), which was adapted from the Li 2019 (46).

5.1.3 Patient population and time horizon in the submitted model

The patient population in the model are adult patients with moderate to severe medication-refractory ET who are ineligible or unwilling to undergo DBS. The start age in the model is 70 years. According to the recruited clinical experts, the start age is reasonable for the

Norwegian setting. The time horizon is sufficiently long to capture relevant differences between the groups.

5.1.4 Efficacy input in the submitted health economic model

Efficacy of unilateral MRgFUS is included in the model in the decision tree. The submitter used the proportion of patients that were characterised as having marked improvement (>50% improvement), mild-to-moderate improvement (10-50% improvement), or unsuccessful procedure (<10% improvement). The proportions were derived from Elias 2016, as illustrated in Figure 5. The proportions are presented in See Table 7.

Table 7. *Proportion of patients with each outcome used in the decision tree inputs for MRgFUS*

Parameter	Proportion	Source
Patients with a marked improvement	48.2%	Elias 2016 (18)
Patients with a mild-to-moderate improvement	42.9%	
Patients with an unsuccessful procedure	8.9%	

The submitter has assumed that after reoperation, the proportions are the same as for the initial procedure.

The probability of reoperation after recurrence is 5% in the model. This is based on Jameel 2022 (expert opinion, Table 2 in Jameel article).

Transition probabilities for the patient cohort after MRgFUS are shown in Table 8. The transition probabilities determine the likelihood of a patient moving from one health state to another during the model cycle (one year). The submitter has assumed a probability of 5 % for reoperation following tremor recurrence. This is the same assumption as made in Jameel 2022.

Table 8. *Probabilities used for the patient cohort after of MRgFUS in the Markov model, adapted from the submission (Excel model and PDF-file)*

Transition in Figure 13	Transition probability	Probability	Source or calculation from the Excel submission with comment by NOMA if applicable.
-	Probability of tremor recurrence	1.36%	Halpern 2019 (20) Elias 2016
P 1.1	Marked improved tremor → Marked improved tremor	90.94%	Calculated as 1 minus probability of leaving the state. 1 - (7.7% + 0.00% + 1.36%)
P 2.2	Marked improved tremor → Mild-to-moderate improved tremor	7.70%	Table 2 from: Jameel 2022 (47) NOMA's comment: this seem to be the probability used by Jameel for DBS for moving form marked improvement to mild improvement due to waning in effectiveness. The probability for MRgFUs (moving from marked to mild number, is 9.2%. Here they refer to Jameel 2022 (48). NOMA was not able to retrieve this number in the mentioned study. However, changing this probability from 7.7% to 9.2% has minimal impact in the end result.

P 1.4	Marked improved tremor → Tremor recurrence (with reoperation)	0.00092%	Calculated as the joint probability of: a) Probability of tremor recurrence b) Probability of reoperation in the event of tremor recurrence. Calculation: 1.36% * 5% * 1.36%
P 1.3	Marked improved tremor → Tremor recurrence (without reoperation)	1.36%	Calculated as the joint probability of: a) Probability of tremor recurrence b) Probability of no reoperation in the event of tremor recurrence. Calculation: 5% * 0.07%
P 2.2	Mild-to-moderate improved tremor → Mild-to-moderate improved tremor	98.64%	Calculated as 1 minus probability of leaving the state: 1 - (1.36% + 0.00%)
P 2.4	Mild-to-moderate improved tremor → Tremor recurrence (with reoperation)	0.00092%	Calculated as the joint probability of: a) Probability of tremor recurrence b) Probability of reoperation in the event of tremor recurrence. Calculation: 1.36% * 5%* 1.36%
P 2.3	Mild-to-moderate improved tremor → Tremor recurrence (without reoperation)	1.36%	Calculated as the joint probability of: a) Probability of tremor recurrence b) Probability of no reoperation in the event of tremor recurrence. Calculation: 1.36% * (1 – (1.36% * 5%)
P 5.5	Baseline tremor → Baseline tremor	100.00%	Assumption: Tremor recurrence without reoperation will result in the patient remaining in the baseline tremor health state for the remainder of the model time horizon, since they do not receive additional treatment.
P 4.1	Tremor recurrence (with reoperation) → Marked improved tremor	48.20%	Assumption: Reoperation is assumed to have the same outcomes as the initial procedure. (Same as in the decision tree) NOMA's comment: In the Excel model, these probabilities were not the same as stated here, but this had negligible impact on the result.
P 4.2	Tremor recurrence (with reoperation) → Mild-to-moderate improved tremor	42.90%	
P 4.5	Tremor recurrence (with reoperation) → Baseline tremor	8.90%	
P 3.5	Tremor recurrence (without reoperation) → Baseline tremor	100.00%	Same as "Baseline tremor → Baseline tremor"
P 2.2	Mild-to-moderate improved tremor (post re-op) → Mild-to-moderate improved tremor	98.64%	Same as above
P 2.3	Mild-to-moderate improved tremor (post reop) → Tremor recurrence (without reoperation)	1.36%	Same as above
P 1.1	Marked improved tremor (post re-op) → Marked improved tremor	90.94%	Same as above
P 1.2	Marked improved tremor (post re-op) → Mild-to-moderate improved tremor	7.70%	Same as above

P 1.3	Marked improved tremor (post re-op) → Tremor recurrence (without reoperation)	1,36%	Same as above

Risk of mortality is included in all cycles. Mortality is determined by age- and gender-adjusted all-cause mortality probabilities for the Norwegian population.

5.1.5 NOMA's comments on the efficacy input in the model

To have a better understanding of the duration of the treatment effect in the model, NOMA has visualised the number of patients in each health state during the time horizon. See Figure 14.

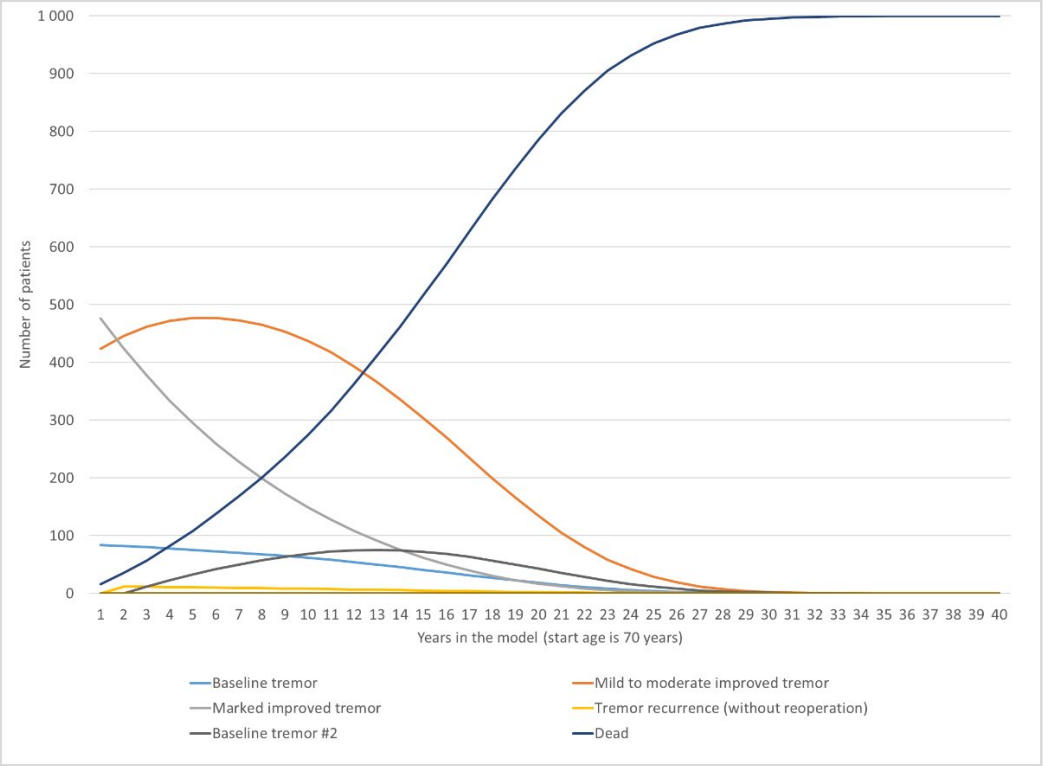

Figure 14. *Visualisation of the how 1000 patients treated with MRgFUS are distributed in the health states over the Markov model time horizon (40 years). Baseline tremor #2 is a health state in the model in which patients enter after they experience tremor recurrence without reoperation, and tremor recurrence with reoperation.*

We also created a graph to show the proportion of patients that are alive in each health state, over the time horizon. This is presented in Figure 15.

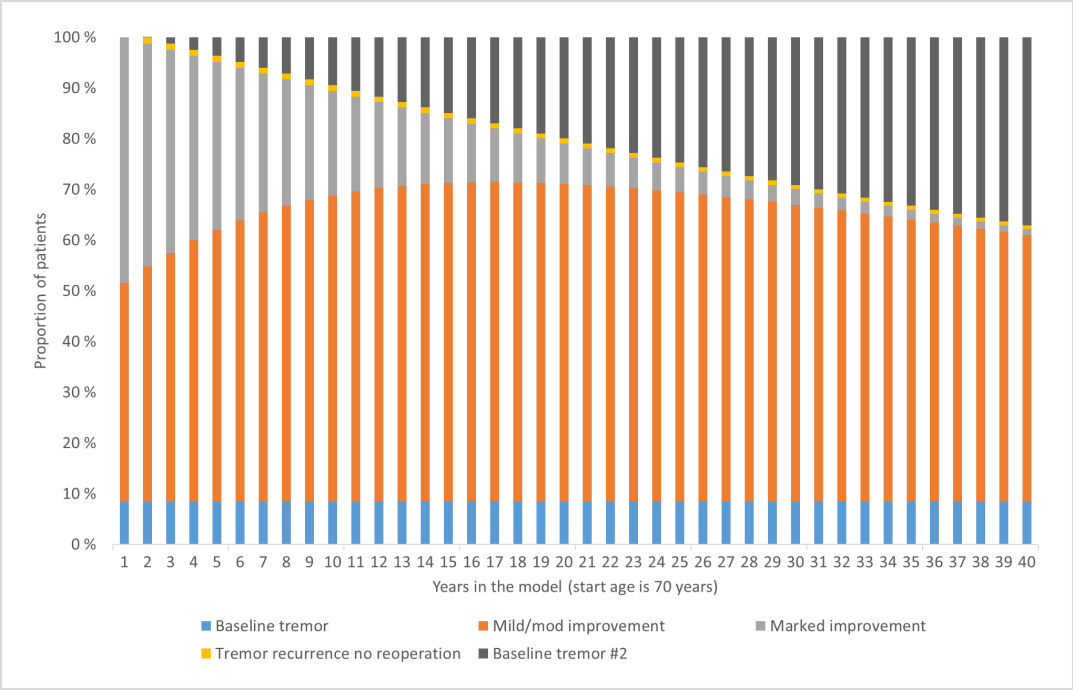

Figure 15. *Distribution of patients in health states who are alive, over the model time horizon*

As described in section 3.3, the RCT Elias 2016 provided robust evidence about the effect of MRgFUS the first three months after the treatment. After three months the sham-group were offered MRgFUS (cross-over), and the treated patients were observed for five years, without a control group (21). Also, non-randomised studies investigated effects of MRgFUS. Some of these had long follow-up periods, but all had a before-and-after design without control group. NOMA has less confidence in the results from studies without control group because these inherently have high risk of bias. The long-term effect of MRgFUS is consequently somewhat uncertain, but the (uncertain) long-term data indicated that the beneficial treatment effects persist one year after treatment. Some studies also suggested that treatment effects may persist beyond one year but observed a trend towards reduced treatment effect with time (Figure 6 andFigure 7).

In the model it is assumed that patients have the same probability of improvement (marked, and mild-to-moderate improvement) after reoperation, as after the first procedure. According to the clinical experts this is a reasonable assumption because it depends on the size of the lesion. They argued that a new procedure with a larger lesion would have at least as good probability for improvement, but possibly somewhat higher risk of adverse events (AE). The proportion of patients that goes through reoperation in the model is a very small. Thus, these probabilities have little impact on the result (ICER).

5.1.6 Inclusion of adverse events in the submitted health economic model

The probability of experiencing specific AE and the duration of these events were included in the model. The included AEs are shown in Table 9.

Table 9. *Adverse events included in the model. Table adapted from the submission.*

Adverse event	Used in model	Source
Short-term stimulation-related AE probabilities		
Probability of gait disturbance (per procedure)	27%	

Probability of paraesthesia or numbness (per procedure)	24%	Health Quality Ontario (49), "Magnetic Resonance-Guided Focused Ultrasound Neurosurgery for Essential Tremor: A Health Technology Assessment", table 24
Probability of speech problem (per procedure)	4%	
Probability of headache (per procedure)	14%	
Long-term stimulation-related AE probabilities		
Probability of long-term gait disturbance (per procedure)	9%	Same as above
Probability of long-term paraesthesia or numbness (per procedure)	14%	
Short-term stimulation-related AE durations (years)		
Duration of gait disturbance	0.2	Same as above
Duration of paraesthesia or numbness	0.4	
Duration of speech problem	0.5	
Duration of headache	0.2	
Long-term stimulation-related AE durations (years)		
Duration of long-term gait disturbance	50	Long-term TRAEs are assumed to be permanent. An arbitrarily large number has been chosen such that the TRAE lasts for the model time horizon.
Duration of long-term paraesthesia or numbness	50	

The AEs seem to be sufficiently in line with the finding in the safety assessment in this STA. However, we do not have exact data on the duration of the long-term AEs. The long-term AEs reported in Elias 2016 are assumed to last for the rest of the persons' life. Two of the non-randomised studies reported a few severe AEs, where one AE (ataxic hemiparesis) persisted during the 12 months study period. See details in section Adverse events in non-randomised studies. NOMA finds it reasonable to not include this AE in the model.

Changing the probabilities of experiencing AEs has minimal impact on the result (ICER).

5.1.7 Health-related quality of life

Health state utility values

The submitter has used health state utility (HSUV) values from Herceg 2012 (50) which is a study investigating efficacy of a medication for ET.

Text from the submission:
"Studies that report utility values for ET are sparse. Some studies assessed the quality of life before and after MRgFUS thalamotomy using the QUEST questionnaire (Elias et al., 2016). However, these values cannot be used to populate health state utility values since we were unable to identify a mapping algorithm that could convert the quality-of-life QUEST scores into utility values. Only one study was identified that measured utility using the European Quality of Life 5 Dimensions (EQ-5D) instrument in people with disabling ET (Herceg et al., 2012)".

The utility for the state "mild-to-moderate tremor improvement" has been assumed to be an average of the "baseline tremor" and the "marked improved tremor" utilities. The submitter assumed that the utility of "tremor recurrence" is the same as that of "baseline tremor". The

decrements are calculated as the difference between “marked improvement” and “mild-to-moderate improvement”, and the difference between “marked improvement” and “baseline tremor”. The utilities applied in the model is presented in Table 10.

Table 10. *Overview of health state utility values copied from the submission*

Health state	Utility	Decrement	Source
Marked improvement	0.91	0	Herceg 2012, visit 5 .
Mild-to-moderate improvement	0.80	0.11	Assumption – a simple average of the baseline and marked improvement utilities.
Baseline tremor	0.69	0.22	Herceg 2012, visit 1

NOMA’s comments on the health state utility values (HSUV)

The utility values used in the submitted model are all based on EuroQol, five dimensions, (EQ-5D) utility scores. EQ-5D is the preferred instrument to measure HRQoL in health economics and health care research according “Guidelines for the submission of documentation for single technology assessments (STAs) of medical devices and diagnostic interventions” (51). The guidelines also state that if other sources than the study used to document clinical efficacy have been used, the submitter should conduct a systematic search for condition-specific utility values.

The submitter has included ”ET AND MRgFUS AND HSUV” in their search. “AND” means that both terms must be present in the studies. Such search would have captured the most suitable treatment-specific utility values, but not necessarily all relevant utility values for the condition ET. This is because the study must also have included MRgFUS to be identified. Thus, we do not know whether a broader search for “ET and HSUV” would have captured other relevant studies on this.

The utility weights are taken form Herceg 2012. This is a small study (N=29) with a follow-up of 16 weeks and mean age is 42 years (±12.5 years). The modelled population’s start age is 70 years, thus the population in the Herceg study is significantly younger. Also, tremor improvement has been measured using another instrument (Fahn-Tolosa-Marin Tremor Rating Scale (FTM)) than that of Eilas 2016. However, this is probably unproblematic, given that FTM is a predecessor of the Clinical Rating Scale for Tremor (CRST) used in Elias 2016. Herceg 2012 used the Hungarian tariffs from the general population for valuation of the EQ-5D health states. NOMA prefers using the UK tariff. The valuation method used is unclear since the article that Herceg 2012 refers to, is in Hungarian (Szende 2003) (52), and only the abstract is available in English, without the information about valuation method used. We did not investigate this further. The EQ-5D version used is the 3L (three level) version. Thus, there are some issues concerning the transferability of the EQ-5D-values from Herceg 2012 to the patient population in this model. However, we acknowledge that EQ-5D data on this patient population is sparse and that the utility values used in this model is likely to be suitable. These have also been applied in other cost-effectiveness models, such as Li 2019 (46) and Jameel 2022 (47).

In the model, patients with “marked improvement” is assumed to have the same quality of life as the general population in that age. The patient association underlines that an improvement on ability to conduct usual tasks (e.g. writing and drinking) will have great influence on independence, self-esteem, mental health, and quality of life in all areas (as

detailed in *Chapter 6. Patient perspective*). However, we do not know whether this is an overestimation for the utility in the submitted model for these specific patients.

NOMA prefers that utility weights are applied as weights, and not as decrements, as described above. We have adjusted this by applying them as weights. Also, to account for increased morbidity and decreased function with increasing age, as well as addressing the discrepancy between the average age from the Herceg 2012 and the model start age, we have age-adjusted the utilities in line with NOMA's guideline for submission of documentation for STAs (51). See the age-adjustments in appendix 7. We have also adjusted the utility weights so that best health state utility in the model ("marked improved tremor") does not exceed the health state utility value of the general population. We followed the multiplicative method as recommended in the guidelines. This resulted in the following utility weights, see Table 11.

Table 11. *Adjusted health state utility values*

Health state	Utility values
Marked improved tremor	0.811
Mild-to-moderate improved tremor	0.713
Baseline tremor	0.615

Adverse event utility decrements

Adverse events (AE) are included in the model as decrements. The average duration and probability of each AE is presented in Table 9. To calculate the utility decrements, the absolute utilities for each event were subtracted from the study utility norm. The decrement was applied for the average duration of the AE. The AE decrements are presented in Table 12.

Table 12. *Overview of AE decrements adapted from the submission*

AE	Absolute value	Study utility norm	Decrement	Source
Stimulation-related AEs				
Motor disturbance	0.77	0.78	0.01	Matza 2019 (53) – time trade-off value for dizziness. Table 4A: Health state utilities associated with the route of administration: Migraine without aura: General population.
Paraesthesia	0.77	0.78	0.01	Matza 2019 – Time trade-off. Table 4A: Health state utilities associated with the route of administration: Migraine without aura: General population
Headache	0.77	0.83	0.06	Van Roijen 1995 (54) – EuroQol descriptive questionnaire. VAS score of 77 for migraine patients and 83 for controls ($p < 0.001$).
Speech problem	0.77	0.78	0.01	Assumption – Assumed to be the same as a motor disturbance, as EQ-5D utility values for speech problems could not be found in the literature.
Long-term AEs				

Motor disturbance	0.77	0.78	0.01	Matza 2019 – time trade-off. Table 4A: Health state utilities associated with the route of administration: Migraine without aura: General population.
Paraesthesia	0.77	0.78	0.01	Matza 2019 –Time trade-off. Table 4A: Health state utilities associated with the route of administration: Migraine without aura: General population.

The utility decrements have been calculated from a study on migraine preventive treatments. They seem reasonable.

5.1.8 Costs and resource use input in the submitted health economic model

The submitter included the following costs in the model: procedure costs (pre, peri and post, including hospitalisation), follow-up costs, annual ongoing medication costs, adverse event costs, and consultations (Table 16). The costs are included in the relevant health states in the model. The health state cost is applied to the percentage of patients in the health state for each cycle.

The costs of the procedure (pre, peri and post) and follow up costs for year 1 are included in the decision tree. Reoperation cost is included in the Markov model in the health state tremor recurrence with reoperation. For reoperations, the following costs were not half-cycle corrected: pre-procedure, peri-procedure, procedure, post-procedure, and follow-up (year one) costs. These costs were assumed to occur at the start of the cycle. Medication costs and follow-up costs from year two are half-cycle corrected.

Unit costs

An overview of the unit costs used in the model by the submitter is shown in Table 13.

Table 13. *Unit costs in the submitted model (table adapted from the submission)*

Parameter	Unit cost / hourly rate (NOK)	Source / comment
Scans		
CT scan	3,290	Unilabs private practice (55) According to the clinical experts, these costs may be an overestimation of the actual cost at the hospital. However, these have minimal impact on the results.
MRI scan	3,890	
Staff (per hour)		
Administrative staff	374	Salary for health secretary. Statistics Norway (56).
Anaesthetist	993	Salary for physician specialist. Salary inflated to the year 2023 (social value). NOMA unit cost database (57).
MRI technician/physicist	566	Salary for radiographer. Keystone Education Group AB (58).
Neurologist	993	Salary for specialised physician. Salary inflated to the year 2023 (social value). NOMA unit cost database.
Neuropsychologist	993	
Neuroradiologist	993	
Neurosurgeon	993	

Nurse: specialist	585	Salary for specialist and non-specialist nurse. Salary inflated to the year 2023 (social value). NOMA unit cost database.
Nurse: non-specialist	546	
Operating department practitioner	330	Salary for cleaning operator (59)
Pharmacist	558	Salary for pharmacist (based on average annual salary (with master's degree + social value). Norges Farmaceutiske Forening. (60).
MRI Physicist	566	Assumes the same as an MRI technician.
Stretcher-bearer	317	Salary for supporting staff (56)
Consultations (per consultation)		
Anaesthetist consultation	822	Specialist consultation unit costs updated to the year 2023. NOMA unit cost database.
Neurology consultation: Face-to-face	4,130	Consultation at the private clinic. Fee for a telephone call consultation, assumed half price of the face-to-face consultation. Sandvika Nevrosenter (61). According to the clinical experts, these costs are probably an overestimation of the actual cost at the hospital. However, this has minimal impact on the results.
Neurology consultation: Telephone call	1,950	
Neurosurgeon consultation	3,266	Taken from the regulation on activity-based financing of hospitals (62). DRG 901O "Poliklinisk konsultasjon vedr andre sykdommer i nervesystemet". (Calculation: 0,066 cost weight multiplied with unit price" of NOK 49,484)
Physiotherapist consultation	800	Fee for the first consultation at private clinic (63)
Radiologist consultation	822	Specialist consultation unit costs have been updated to the year 2023. NOMA unit cost database.
Specialist nurse consultation	585	Specialist nurse consultation unit costs have been updated to the year 2023. NOMA unit cost database
Lab tests		
Blood test	141	Unit cost. Has been updated to the year 2023. NOMA unit cost database.
Other		
Cleaning solution per procedure	5	Assumption

Cost and resource use of MRgFUS

Cost of the MRgFUS device

The cost of MRgFUS was provided by the submitter. The device cost is NOK [redacted] per device. A patient kit used per procedure is NOK [redacted]. Assumed lifetime uses was 500.

NOMA added device amortisation costs to the per-case cost. To calculate the amortisation, we used the Excel function which calculated depreciation for the asset using a straight-line depreciation method, over a 10-year period, applying the annual discount rate of 4% (see details in Appendix 8). This resulted in yearly amortisation cost of NOK [redacted]. Assuming the utilisation rate of 50 procedures per year, the device cost per case resulted then in NOK [redacted]. To that we also added overhead costs of 15%. This resulted in a MRgFUS device cost of NOK [redacted] per procedure.

Maintenance costs for MRgFUS

According to the submitter, *"the maintenance cost was calculated as a cost per case, considering a ten-year lifetime with one year of free maintenance. The yearly cost was multiplied by the number of years paid, i.e., nine years, and then divided by the lifetime (ten years), which provided an average annual cost accounting for the free year. The cost per case was calculated by dividing this cost by the annual caseload (assumed to be 50)."* See Table 14.

Table 14. *Maintenance cost of MRgFUS copied from the submission with minor adaptations*

Resource	Unit cost (NOK)	Source	Per case cost (NOK)	Notes
Maintenance cost	[redacted]	Provided by Insightec. Assumed device lifetime of ten years.	[redacted]	Annual caseload assumed to be 50

If the caseload would be higher, the maintenance cost per case would be lower. E.g. if the caseload would be 100 procedures per year, the maintenance cost per case would be NOK [redacted]. Thus, NOK [redacted] is a conservative assumption.

Resource use of MRgFUS

The submitter assumed the following resource use in connection with the MRgFUS procedure. See Table 15.

Table 15. *Resource use in connection with MRgFUS, information adapted from the submission*

Phase	Resource use
Before the procedure	• The patient will undergo one CT, one MRI, and an assessment test to evaluate their suitability for the procedure (conducted by a specialist nurse, anaesthetist consultation, and a neurosurgeon consultation. • Admission and routine tests: 1 hour with a neurosurgeon, radiologist, or neuroradiologist.
The procedure itself	• Shaving the patient, 30 minutes (nurse) • System testing, 45 minutes (MRI technician, physicist) • 1 hour for preparations in the MRI area (frame placement, IV, and monitoring) involving a nurse, MRI technician, neurosurgeon, and 30 minutes for a neurologist. • Procedure: 2 hours involving a neurosurgeon, neurologist, MRI technician, nurse, and operating department practitioner. 20 minutes for a porter. • 1 hour of immediate post-procedure care involving a nurse, neurosurgeon, neurologist, and MRI technician.
After the procedure	• The patient undergoes a new MRI, neurological evaluation, and will be discharged the day after the procedure
Yearly	• One face-to-face neurology consultation

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; IV, intravenous

The recruited clinical experts confirmed that the assumptions on resource use are reasonable for the Norwegian clinical practice. But, according to clinical expert input, it is possible to perform MRgFUS as an outpatient procedure, however it may be appropriate to

admit the patient the day before, at least for those traveling to the hospital from other cities/regions many will be admitted to the hospital the day before the MRgFUS procedure and discharged the day after. Therefore, we have updated the number of stays (days) in standard ward from 1 to 2 (two nights).

Summarised cost related to the MRgFUS procedure

Table 16 shows a summary of the costs related to the MRgFUS procedure. A detailed overview of the costs and resource use in each element can be found in Appendix 8.

Table 16. *Summary of costs related to the MRgFUS procedure (updated costs, table adapted from the submission)*

Element	Cost used in the model (NOK)
Pre-procedure costs (1–2 months prior to surgery)	16,571
Peri-procedure costs (day of surgery exc. procedure)	5,354
Procedure costs (excluding maintenance costs)	[redacted]
Maintenance cost per case	[redacted]
Post-procedure: hospital stay, recovery, discharge	49,865
Follow up costs (year 1)	14,100
Follow up costs (year 2+)	4,130

With the abovementioned costs, the total cost of one MRgFUS procedure would entail around NOK [redacted] (not included follow-up costs). This includes a cost of using the MR-scanner per procedure (as presented in Table 13), overhead costs of 15% on personnel costs and the device cost.

Costs and resource use of comparator 'no procedure'

The patient cohort has two yearly face-to-face neurology consultations, ongoing medication. See more on medication use in section "Costs of ongoing medication".

Costs of ongoing medication

In the submitted analysis the cost of ongoing medication was NOK 7,590 per year. These medications are propranolol, primidone, topiramate, and alprazolam. These costs can be found in Appendix 8.

According to the clinical expert input, propranolol is the first choice in Norway, and primidone is the second choice in ET treatment. The patients must usually have tried both of these medications before being considered for advanced treatment (DBS or MRgFUS). The experts also state that many patients try topiramate, which may have a tremor-reducing effect in some cases. And, that alprazolam is not used in standard and recommended ET treatment in Norway (64).

The clinical experts argued that it is not reasonable to expect that patients will use all these medications after MRgFUS. Further, they stated that for the indication medication-refractory tremor, most patients due to poor symptomatic effect, will often use only one medication, or none, when they are considered for the advanced treatment. After advanced treatment, some patients will continue with their previous medication at the same or a reduced dose, while others may stop entirely if the tremor improves sufficiently from the procedure (64).

One study on medication use after DBS for tremor showed that 91 %, i.e. 31 persons, stopped using anti-tremor medications after the surgery (65). This might be similar for MRgFUS patients, but we do not know. Since we do not have data on medication use after MRgFUS, and for the no procedure group, we assumed that 50% of patients that have undergone MRgFUS uses one medication (propranolol). This may be an overestimation. We have assumed that 75% of patients in the no procedure group uses one medication (propranolol). We have included these costs in the revised analysis. This may also be an overestimation.

In Elias 2016, the patients had to be refractory to at least two trials of medical therapy, (either propranolol or primidone). If the patients received medication while undergoing MRgFUS, the doses had to have been stable for 30 days prior to randomisation. This fits well with the assumed medication use in the model.

Health state costs in the submitted Markov model

The health state baseline tremor in the comparator cohort, no procedure, has an annual cost of NOK 12,382. This cost includes two face-to-face neurology consultations, and medication.

Annual (cycle) health state costs for MRgFUS are listed in Table 17.

Table 17. *Annual health state costs for MRgFUS in the Markov model*

Health state	NOK	Comment
Baseline tremor	6,878	Includes one face-to-face neurology consultation, and ongoing medication
Mild-to-moderate improved tremor	6,878	
Marked improved tremor	6,878	
Tremor recurrence (without reoperation)	6,878	
Mild-to-moderate improved tremor #2	6,878	
Marked improved tremor #2	6,878	
Tremor recurrence (without reoperation) #2	6,878	
Baseline tremor #2	6,878	
Tremor recurrence (with reoperation)	[redacted]	Includes pre-, peri- and post-procedure costs, maintenance, follow-up costs year 1, and ongoing medication

5.1.9 Calculation of severity – absolute shortfall

The submitter estimated absolute shortfall (AS) based on projections about life expectancies. The AS calculation follows the guidelines for the submission of documentation for single technology assessments of medical devices and diagnostic interventions (51). These guidelines are based on the white paper (Meld . St . 34 (2015–2016)) to Parliament on priority setting (44), as well as a Norwegian life table and age-adjusted HRQoL data from the general Swedish population (51).

AS represents the difference between quality-adjusted life expectancies at a specific age (A) without the presence of the disease ($QALYs_A$), and the prognosis with the disease while receiving the current standard of care (P_A).

$$AS = QALYs_A - P_A$$

For the calculations, the submitter employed undiscounted numbers for $QALYs_A$ and P_A as indicators of prognosis.

5.1.10 One-way sensitivity analysis

The submitter conducted a series of one-way sensitivity analyses to explore the impact of individual parameter uncertainties on the cost-effectiveness result. A list of parameters used for the one-way sensitivity analyses is presented in Appendix 9. One-way analyses were conducted on the net monetary benefit (NMB) metric, which is defined as the product of incremental quality-adjusted life years (QALYs) and the willingness-to-pay threshold (WTP), minus the incremental cost. The input parameters were varied by 15%. The submitted analyses assumed a WTP value of NOK 500,000 per QALY. The results of these analyses are illustrated in the form of a tornado diagram in the results chapter.

5.1.11 Budget impact analysis

Budget impacts are defined as additional costs, i.e. the total expenditure of introducing the technology minus the total costs of not doing so. In a budget impact analysis (BIA), the budget impacts for the specialist health services in a national perspective are to be calculated. The recommended time horizon for drugs is five years. For other products, the time horizon varies depending on the product's useful life or depreciation. The submitter has used a horizon of five years and calculated budget impacts for a scenario where MRgFUS is introduced vs. a scenario where it is not introduced.

Text copied directly from the submission:
"Costs were estimated over a five-year time horizon. An annual cycle length was used to derive all outputs for each setting. The calculated annual costs were not discounted. The cost inputs were derived from the cost-effectiveness model described in the previous sections of the report. The costs are linked from the decision tree for the first year and from the Markov traces MRgFUS, "…" and SoC[1] for the remaining four years.

The MRgFUS maintenance cost in the first year was set to zero for newly installed devices (as informed by Insightec). For the following years, the annual maintenance cost was applied to the number of new devices…"

The submitter has assumed that 30 patients will undergo MRgFUS in year 1, 50 patients in year 2, 60 patients in year 4 and 100 patients in year 5. And, that two MRgFUS devices are to be implemented in Norway (in Trondheim and Oslo where DBS is currently performed). According to one of the recruited clinical experts, the assumed number of patients in year one is substantially lower than the number of ET patients waiting for treatment in Norway. One of the experts estimated that 50 ET patients may be treated with MRgFUS yearly, in the long-term. The expert also estimated that 30% of patients that have undergone unilateral (one-sided procedure), will need to be treated on the other side in a separate procedure (bilateral procedure). Taking this into account, the annual number of MRgFUS procedures for patients with ET could be 65 in the long term (50 * (1 + 30%)).

The experts confirmed that it is reasonable to assume that two procedures can be performed in one day. We assumed a gradual implementation. Based on the experts' input, we have used the yearly number of MRgFUS procedures shown in Table 18 in the BIA.

[1] SOC, standard of care (no procedure)

Table 18. *Annual number of MRgFUS procedures for patients with ET*

Year 1	Year 2	Year 3	Year 4	Year 5
50	60	65	65	65

We have conducted one analysis where one MRgFUS device is implemented in year one, and a second analysis where two MRgFUS devices are implemented in year 1.

Value added tax (VAT) has been included in the BIA according to the guidelines for submission (51). The procurement cost of the MRgFUS device(s) is included up-front. Thus, this cost is included in year 1. The cost of medication and yearly consultation after MRgFUS is included the following years for these patients.

The BIA inputs can be found in Appendix 11.

5.2 Results

In this chapter we present the results of the submitted analyses base case analysis, and NOMA's revised analyses. The result of the submitted base case analysis is presented in Table 19. The submitter assumed a WTP threshold of NOK 500,000. This is used for the NMB calculation as discussed in 5.1.10.

5.2.1 Base case analysis

The results of the submitted base case analysis are presented in Table 19.

Table 19. *Results of the submitted cost-effectiveness analysis*

	MRgFUS	No procedure	Incremental
Costs per person	NOK 328,155	NOK 87,881	NOK 240,274
QALYs per person	7.354	6.048	1.306
Total life years per person	10.63	10.63	0.00
Incremental cost-effectiveness ratio (ICER)			**NOK 183,963**
Net monetary benefit (NMB) per person			NOK 412,779

Abbreviations: QALY, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio

The results of the base case analysis after NOMA's revisions are presented in Table 20.

Table 20. *Results from the revised analysis by NOMA*

	MRgFUS	No procedure	Incremental
Costs per person	NOK 330,899	NOK 131,738	NOK 199,161
QALYs per person	6.210	5.159	1.051
Total life years per person	10.63	10.63	0.00
Incremental cost-effectiveness ratio (ICER)			**NOK 189,492**
Net monetary benefit (NMB) per person			NOK 326,353

Abbreviations: QALY, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio

This analysis by NOMA includes ongoing medication in the no procedure group, and the medication use has been updated according to clinical expert input. The analysis includes also amortisation and overhead cost of the device and personnel, and cost of MR-scanner use during the procedure. Also, the utility weights were adjusted by NOMA. This makes the QALY gain lower (in both groups), but the result of the absolute shortfall calculation (severity), higher.

5.2.2 One-way sensitivity analysis (revised analysis)

Figure 16 presents the tornado diagram of the one-way sensitivity analyses. A positive incremental NMB indicates that the intervention is cost-effective compared with the alternative at the assumed willingness-to-pay threshold of NOK 500,000 (66).

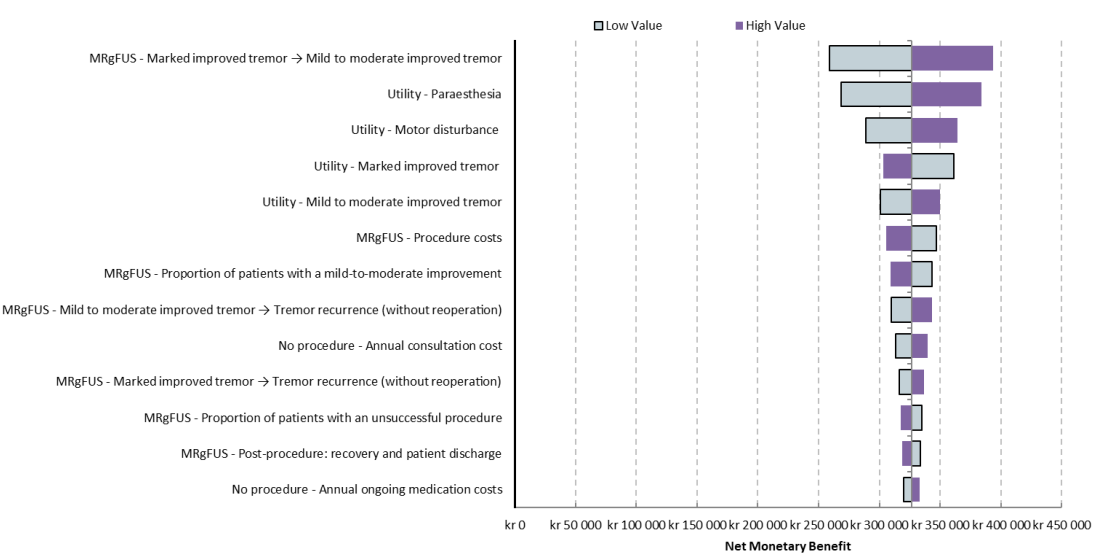

***Figure 16**. Tornado diagram illustrating the results of the one-way sensitivity analyses.*
***Abbreviations:** NMB, net monetary benefit; kr, Norwegian krone*

From the tornado diagram we can see that the probability of going from health state “marked improved tremor” to “mild-to-moderate improved tremor” has the greatest impact on the NMB. The parameters that have second, and third greatest impact on NMB are utility associated with paraesthesia and motor disturbance. The utilities in health states “marked improved tremor” and “mild-to-moderate improved tremor” have the fourth and fifth most impact.

If the bars cross the line of NOK 0 NMB (indicated by black line), MRgFUS is no longer cost-effective given the WTP threshold of NOK 500,000. This was not the case for any of parameter variations.

A table showing the parameters’ minimum and maximum values which was used in the one-way sensitivity analysis is presented in Appendix 9.

5.2.3 Severity calculation – absolute shortfall

In the submitted economic model, patients are assumed to enter the model at the age of 70. At this age, the expected quality-adjusted life expectancy for the general population is estimated to be 13 years (51). Considering the disease prognosis, the expected QALYs for patients in the no procedure group is estimated to be 6.2 QALYs, after NOMA’s adjustments. The absolute shortfall under these assumptions is presented in Table 21.

Table 21. *Calculation of absolute shortfall*

Explanation	Expressed as	Years / QALYs
Average age at the start of treatment	A	70
Expected remaining QALYs (undiscounted) for the general population without the disease	$QALYs_A$	13.0
Expected remaining QALYs (undiscounted) for those with the disease and without the new test (that is, prognosis of patients treated with current standard treatment))	P_A	6.2
Number of QALYs lost due to disease (absolute shortfall)	AS	6.8

As outlined in the white paper to Parliament on priority setting (44), the benefit criterion and resource use criterion is to be assessed in relation to the severity in priority setting. The more severe a condition is, the higher resource use is acceptable. Cost-effectiveness threshold should be adjusted based on the severity categories proposed by the Norheim and Magnussen commissions. These categories suggest that conditions with an expected QALY value below 4 belong to the least severe group, while those exceeding 20 QALYs are considered among the most severe.

5.2.4 Budget impact

The result of the budget impact analysis with one device implemented in year 1 is presented in Table 22.

Table 22. *Results of the budget impact analysis with one device, rounded in NOK (including VAT)*

Scenario	Year 1	Year 2	Year 3	Year 4	Year 5
Budget with MRgFUS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget without MRgFUS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The total budget impact over the five-year period, with one device implemented, is around NOK [redacted] million.

The result of the budget impact analysis with two devices implemented in year 1 is presented in Table 23.

Table 23. *Results of the budget impact analysis with two devices, rounded in NOK (including VAT)*

Scenario	Year 1	Year 2	Year 3	Year 4	Year 5
Budget with MRgFUS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget without MRgFUS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The total budget impact over the five-year period, with two devices implemented, is approximately NOK [redacted] million.

6. Patient perspective

NOMA reached out to the patient association "*Essensiell Tremor-Foreningen Norge"* to obtain information on the patient perspective. We disseminated an adapted version of the patient input questionnaire developed by the Health Technology Assessment International (HTAi) (67). The questionnaire was answered by the association Chair in September 2024.

"*Essensiell Tremor-Foreningen Norge*" is a non-profit association for people with ET and was established in January 2023. According to Chair, the association received a startup grant of NOK 40,000 from Insightec. The association recently conducted a survey for persons with ET (November 2023–April 2024). The survey received 153 responses, where 140 of the respondents were diagnosed with ET. The age and disease duration of the respondents varied substantially, and the majority were women (78%). The association used the survey to answer our questionnaire. The entire survey including more details about the respondents can be found on the association's website (68).

The questions (Q1–Q7) and the answers to NOMA's questionnaire are presented below.

Q1. How does the condition or disease affect the patients' quality of life?

The association's survey revealed that 43% (63/146) of respondents began experiencing ET symptoms before the age of 20. An additional 12% (18/146) identified symptoms between the ages of 20 and 29. The association explained that although the tremors were likely mild at their onset, they could lead to psychological and social impacts. Given that ET is a progressive condition, most individuals would experience a worsening of their tremors and a decline in function over time.

The ability to enjoy or participate in hobbies or activities could be compromised by tremors, especially activities that require fine motor skills such as arts, crafts, and needlework. In the survey, 66% (79/120) of the respondents indicated that they occasionally or frequently lost interest in hobbies or activities due to tremors. Sixty-seven percent (80/120) reported that they occasionally or frequently abandoned hobbies or activities for the same reason.

The survey revealed that 62% (71/115) experienced depression occasionally, frequently, or constantly due to their tremors. The association suggested that this could be due to reduced self-esteem following challenges in performing daily tasks and increased need of assistance. Seventy-four percent (85/115) of the survey respondents felt fatigued frequently or always. The association suggested that the energy required to manage muscle tremors could cause fatigue, reduce work capacity, and impair overall quality of life.

In the survey, 11% (16/150) of respondents indicated that they were retired or received disability benefits due to ET. The association argued that many individuals could benefit from effective treatment to enhance their work capacity and efficiency, both professionally and during their leisure time.

Q2. How does the condition affect relatives?

The association's survey did not ask specific questions about next of kin. However, the association explained that many concerns experienced by patients, such as anxiety about worsening tremors and loss of functionality, are likely to be shared by their relatives. Family members may need to assist with or assume tasks that become challenging due to tremors, such as household chores (washing dishes, cooking, etc.), or personal hygiene in more severe instances (buttoning clothes, shaving, etc.). Additionally, the association highlighted that prior to a definitive diagnosis, the presence of tremors can generate worry and uncertainty about their underlying cause.

Q3. Are there groups of patients who particularly have difficulty managing the condition?

The association explained that ET is generally not well-understood, even among healthcare professionals. Groups with limited access to healthcare services, or those facing barriers such as language difficulties, may have larger difficulty obtaining a diagnosis, and may thus have particular difficulty managing the condition. The association also emphasised that social stigma substantially impacts those with ET. Individuals with ET face a double burden in societies where physical and/or mental disorders are heavily stigmatised.

Q4. How well do patients manage the condition with existing treatments?

Beta-blockers and antiepileptic drugs serve as the first and second-line treatments for ET. The association explained that fatigue and dizziness are common side effects of these medications. According to the association's survey, 31% (20/65) of the respondents expressed complete dissatisfaction with the effectiveness of these drugs. A small proportion of 8% (5/65) reported a high level of satisfaction with these treatments. The association emphasised that tremors could cause difficulties for patients, such as struggling to remove pills from jars or wrappers, or dropping them on the floor. The association also referred to anecdotal evidence from Facebook groups, indicating that many doctors lack proper knowledge about correct drug dosing. Reportedly, some patients have received excessively high initial doses with inadequate or no escalation. According to the association, this practice could lead to an increase in side effects.

Botulin toxin (Botox) injections in the neck and/or shoulders is a potential treatment method that may help manage tremors in the neck, shoulders, and arms in some cases. Twenty-seven of the survey respondents had received Botox injections. Twenty-one respondents were somewhat satisfied or satisfied with the treatment whereas five were dissatisfied. The association added that this treatment can have side effects, including loss of sensation in the fingers or headaches.

Deep Brain Stimulation (DBS) is a surgical treatment for ET. The association emphasised that the invasive nature of DBS can be daunting for patients. The association underscored the potential risks of the procedure, including infection and complications that can arise from the surgery, during which the skull is opened, and electrodes are inserted through healthy brain tissue to reach the thalamus. Furthermore, the association explained that the electrodes may displace either during the procedure or afterward. This may reduce the effect and may require a subsequent surgery for correction. In the association's survey, 12% (13/113) of respondents expressed an interest in undergoing DBS treatment, 30% (34/113) stated they did not want it, and 39% (44/113) were unsure about whether they wanted it or not. A smaller fraction of 6% (7/113) had already undergone DBS treatment, while 13% (15/113) responded that the question was not relevant to them.

Q4. Are there groups of patients who have difficulties in using existing treatment?

The association highlighted potential issues related to the use of beta-blockers, particularly for individuals with already low blood pressure. The association cautioned that beta-blockers can further decrease blood pressure and potentially cause dizziness or fainting. Additionally, the association suggested that antiepileptic drugs may interfere with the effectiveness of hormonal contraceptive pills. Consequently, hormonal birth control pills may not provide reliable contraception when used in conjunction with these drugs.

Q5. What are the expectations and limitations of the technology under investigation?

The HTAi questionnaire provides two options to capture experiences with the technology under assessment. The options are a) for those who have experience with the technology, and b) for those who lack experience with the technology. The answers from the patient association were grounded in option b.

The association argued that studies show a significant reduction in tremor following treatment with MRgFUS. They noted that in some instances, individuals who previously could not write by hand or hold a full glass to drink were able to perform these tasks without difficulty following MRgFUS. The association pointed out that such effects can substantially enhance independence, self-esteem, and mental health (by reducing depression and anxiety) and improve overall quality of life. They emphasised that these improvements also can positively impact caregivers. Furthermore, the association argued that reducing tremors, even if only on one side of the body, can enhance the ability to perform tasks that are challenging due to tremors. Having one steady hand is considerably better than none and having two is even more beneficial for many tasks. The association explained that for those with moderate to severe ET, a reduction of 50-70% would have a major impact and improve functional abilities in many areas.

The association asserted that the benefits of MRgFUS over DBS include its non-invasive nature, which reduces the risk of infection and damage to healthy brain tissue while reaching the thalamus and obviates the need for follow-up surgeries for battery replacement or electrode adjustments. When compared with medication-based treatments, The association considered both MRgFUS and DBS to present the advantage of offering long-term or permanent relief. Consequently, patients are not required to take pills multiple times a day or undergo Botox injections every three months.

The association suggested that potential disadvantages of MRgFUS compared to DBS include the greater flexibility offered by DBS to adjust the treatment by altering the electrical impulses at later time points. In contrast, MRgFUS aims to treat the ET as it presents at the time of treatment with minimal recovery time. The association further suggested that patients might possibly hesitate to undergo MRgFUS treatment due to apprehensions about undergoing brain surgery, even a non-invasive one. However, the association argued that MRgFUS is associated with low risk of complications or side effects but acknowledged that such risks are not entirely absent.

Q6. Which groups of patients can benefit most from the method under assessment?

The association explained that patients with significant ET who witness little to no improvement from medications might benefit from MRgFUS. Furthermore, they suggested that individuals whose work capacity has been substantially impaired due to tremors could also potentially benefit from this treatment.

Q7. What are the main messages?

The patient organisation was encouraged to articulate the most important points they wanted to emphasise. The main messages were as follows:

- The most significant challenge with ET is the impact on all hand-related activities, ranging from eating and drinking to signing documents and online banking.
- Current treatments fall short, as approximately 50% of patients see no improvement from medications.
- The advantages of MRgFUS are the considerable tremor reduction, the non-invasive nature, and the minimal recovery time.

7. Discussion

7.1 Discussion – clinical effectiveness

7.1.1 Key findings

One multicenter RCT with 76 patients and 13 non-randomised studies with 1,029 patients (in total) were included. All studies investigated patients with medication-refractory, moderate to severe ET. The multicenter RCT compared MRgFUS with sham and was conducted in USA, Canada, South Korea, and Japan. The non-randomised studies compared pre- and posttreatment scores (no control group) and were conducted in USA, Japan, Spain, Italy, China, Australia, Germany, and Israel.

Three months after the treatment, we found that MRgFUS:

- reduced hand tremor (high certainty)
- reduced disability (high certainty)
- probably improved quality of life (moderate certainty)

The beneficial treatment effects may persist one year after treatment (low certainty). Whether treatment effects persist beyond one year is hard to judge based on the available documentation (very low certainty).

MRgFUS was also associated with adverse events. The adverse events were common, but mostly mild and transient. The most common adverse events were “paresthesia or numbness” and “gait disturbance”. These events occurred in more than one third of the patients and persisted one year after the treatment in about one tenth of the patients.

7.1.2 Evidence quality and limitations

All the included studies investigated patients with medication-refractory, moderate to severe ET. There were more men than women in the studies which probably reflects a higher prevalence of ET among men. The mean or median age of the patients varied from 62 to 75 years and the average disease duration varied from 13 to 30 year. These ranges are comparable to the population that can be expected to undergo MRgFUS in Norway, and consequently the reported results should be relevant for Norway.

One multicenter RCT compared the effect of MRgFUS with that of sham. The RCT was well designed, and risks of bias were deemed to be low during the first three months after treatment. Our certainty in the results was high and moderate, but it remains a weakness that only one RCT evaluated the effect of MRgFUS for the relevant population. We also included 13 non-randomised studies, and the results from these aligned well with the results from the RCT. This represents an important strength.

Patients that were randomised to sham were offered MRgFUS after three months (in the included RCT). Results obtained from the uncontrolled and unblinded extension phase were combined with results from non-randomised studies in our report. Our certainty in these results was low or very low because the non-randomised design of the studies inherently caused high risk of bias. In several of the studies, a substantial number of patients was also lost to follow-up at late time points which further increased the risk of bias. The duration of the treatment effect (beyond three months) is therefore uncertain, and this represents a major limitation.

The number of patients in the included RCT was based on a power analysis considering the effect on hand tremor score assessed in a prior pilot study (18). Accordingly, the number of

patients was sufficient to detect significant differences in hand tremor score. The number of patients was also sufficient to detect significant differences in disability score and quality of life, and sufficient to identify several common adverse events. However, the number of patients was not powered to identify adverse events that may occur rarely. Although most adverse events identified in the current report were mild and transient, we cannot rule out the possibility that MRgFUS may induce rare adverse events that can be severe.

7.1.3 Consistency

NOMA identified three HTAs that evaluated MRgFUS for essential tremor. The HTAs were conducted by the Austrian Institute for Health Technology Assessment in 2023 (16), HTA Syd in Sweden in 2023 (17), and Health Quality Ontario in Canada in 2018 (15). All the HTAs included the RCT Elias 2016 but did not identify additional RCTs. The Swedish HTA only included RCTs, whereas the Austrian and the Canadian HTAs also included non-randomised studies. In contrast to the current report, the Austrian and the Canadian HTA did not exclude non-randomised studies with very few patients. Despite these methodological differences, the three HTAs agreed that MRgFUS improved hand tremor, disability, and quality of life three months after the treatment. The HTAs also found that adverse events associated with MRgFUS were mild or moderate, and pointed out that treatment effects beyond three months were uncertain because of the non-randomised designs of the available studies. The three HTAs thus align well with the findings of this report.

7.2 Discussion – health economic evaluation

7.2.1 Key findings

The base case cost-effectiveness analysis indicates that unilateral MRgFUS for patients with moderate to severe medication-refractory ET provides more QALYs, but at a higher cost than the comparator ‘no procedure’. The incremental cost-effectiveness ratio (ICER) was approximately NOK 189,000 per QALY. The result remained robust in the sensitivity analyses. However, there is uncertainty associated with the treatment effectiveness duration and the utilities applied. There is also uncertainty related to other parameters. We discuss these issues below.

Implementation of one MRgFUS device could entail a budget impact of around NOK [redacted] million over five years. Implementation of two devices could entail a budget impact of approximately NOK [redacted] million, also over five years. In the analyses, the device cost is included in year 1.

7.2.2 Limitations and uncertainties

The one-way sensitivity analyses showed that the probability of moving from health state “marked improved tremor” to “mild-to-moderate improved tremor”, have the greatest impact on the result. The parameters that have second, and third greatest impact on the result are utility associated with paraesthesia and motor disturbance. These are the long-term adverse events. The utilities in the health states “marked improved tremor” and “mild-to-moderate improved tremor” have the fourth and fifth greatest impact. There is uncertainty related to the utilities in the model, as discussed in 5.1.7. However, the result remained robust when changing the parameters one by one with 15% (see tornado diagram). When increasing all utility decrements by 15%, the ICER increased by around NOK 48,000.

One of the main uncertainties in the model is the duration of the treatment effect. The treatment effect duration is jointly affected by several parameters. The parameters are mainly probabilities for:

- moving from “marked improved tremor” to “mild-to-moderate improved tremor”
- moving from “mild-to-moderate improved tremor” to tremor recurrence (without reoperation)”
- moving from “marked improved tremor” to tremor recurrence (without reoperation)”
- staying in “marked improved tremor”
- staying in ““mild-to-moderate improved tremor”

To explore this, we did a test where we increased the probability of tremor recurrence from 1.36% to 10% in the model. This decreased the probability of remaining in “marked improved tremor” from 90.9% to 82.3%, and the probability of remaining in “mild-to-moderate improved tremor” from 98.6% to 90.0%. The increased probability of tremor recurrence resulted in an ICER of around NOK 276,000 per QALY. The number of persons in the health states at year 10 (80 years old) would then be (probability of recurrence of 10%):

- 468 persons in baseline tremor health state(s)
- 196 persons in mild-to-moderate improvement
- 61 persons in marked improvement

For comparison, in NOMA’s base case analysis (probability of recurrence of 1.36%):

- 138 persons in baseline tremor health state(s)
- 437 persons in mild-to-moderate improvement
- 149 persons in the marked improvement health state

The submitter conducted probabilistic sensitivity analyses (PSA). We ran a new PSA after the revisions. These analyses indicate that MRgFUS has a likelihood of 99,6% of being cost-effective compared to no procedure, assuming a WTP threshold of NOK 275,000 per QALY. See details on the PSA in Appendix 9.

The start age in the submitted model was 70 years. Our clinical experts argued that the start age may be too high, particularly when patients that are unwilling to undergo DBS are included. NOMA changed the start age in the model to 62 years. This resulted in an ICER of NOK 143,000 (in comparison to the ICER of NOK 189,000 which was found in the analysis with a start age of 70 years).

Patients with ET will usually experience progression of the condition over time. This is not captured in the model for the no procedure group, which may overestimate the QALYs gained in this group. The decrease in health-related quality of life with increasing age in general is however included. Also, the model does not include the need for municipal services that some patients with ET might need (non-health services are outside the analysis perspective). This is because the health economic evaluations uses an extended healthcare perspective, in accordance with principles in the white paper to Parliament on priority setting (69). Thus, for example lack of ability to work (production loss), and other elements in a societal perspective, are not included in the analysis. It is however worth to mention that follow-up investigations of the participants in Elias 2016 found significant improvements in the QUEST subdomain “Work and finance subscore”, indicating improved ability to work after MRgFUS (21).

If MRgFUS is implemented, there would be an increased demand for MRI capacity to perform the procedure alongside all other applications of the MR-scanner. The unit cost of MR-scanning is included in the analysis, but not the costs of acquisition of any additional MR-scanners or employing additional staff to operate them.

Also, the investment costs of implementing MRgFUS are relatively high. The actual cost per MRgFUS procedure is dependent on the number of procedures that are performed yearly, i.e. how many procedures the large investment cost is spread out on.

The unit costs for CT scan, and neurology consultation (face-to-face and telephone) might be overestimated. However, these costs have minimal impact on the result (ICER). In the analysis, we have assumed that 50% of the patients will use one medication after MRgFUS, and that 75% will use medication in the no procedure group. According to the clinical experts, the assumed proportion of medication users after MRgFUS might be too high. We lack data on this. The proportion of medication users in the no procedure group may also be overestimated or underestimated. If we decrease the proportion of medication users in the MRgFUS group, the ICER decreases. And conversely, if we decrease the proportion of medication users in the no procedure group, the ICER increases. However, no plausible changes to the proportions alone change the conclusion.

In the budget impact analysis (BIA), we have estimated the number of patients who may undergo MRgFUS the next five years. These are patients with moderate to severe medication-refractory ET, who are ineligible or unwilling to undergo DBS. The estimated number of patients is based on expert input. The expert also stated that patients with medication resistant tremor, with the same symptoms, but with another or uncertain diagnosis can be relevant for MRgFUS treatment. Utilisation of MRgFUS infrastructure by these patients would potentially have an impact on both capacity and the unit cost of the procedure. However, patients with other indications than ET and the potential impact were not included in our analyses because these are beyond the scope of the current STA.

The clinical experts argued that it is important to implement MRgFUS in at least one location in Norway, and that the need may be sufficient to justify two locations in the long term. The cost of training personnel was not included in the cost-effectiveness analysis or the BIA. If MRgFUS is offered in two locations, the cost of training would be approximately double. Maintenance costs would also be doubled with two devices. This is however included in the analyses. If we assumed that two MRgFUS devices is to be implemented, the number of yearly procedures could have been higher than estimated in the budget impact analyses, due to higher capacity. The economic analyses in this STA are based on the assumption that sufficient infrastructure (MR-scanners and trained staff) is in place for introducing MRgFUS. The potential need for expansion of this capacity and associated costs are not accounted for in any of the analyses.

In the BIAs the device cost was included up-front, in year 1. If the device cost was spread out across patients, the budget impact per year would be approximately NOK [redacted] m, [redacted] m, [redacted] m, [redacted] m, [redacted] m, and the total budget impact would be around NOK [redacted] m over the first five years (analysis with one device). Amortisation costs are not applied here.

7.2.3 The cost of the procedure abroad

According to the Foreign Office at Oslo University Hospital (“Avdeling for utenlandskontor og behandlingsreiser”), some Norwegian patients have received MRgFUS in Denmark. The invoiced cost for the procedure in Denmark was NOK 273,791 in 2022. This cost did not include travel and accommodation. Unfortunately, the hospital in Denmark cannot treat Norwegian patients any longer. The Foreign Office has looked for other locations in Europe where Norwegian patients could undergo MRgFUS, but most countries offering MRgFUS have limited capacity and waiting lines for their own population. According to the Foreign Office, many countries are therefore unwilling to accept patients from other countries (70).

In comparison, the estimated cost MRgFUS in Norway was around NOK [redacted] per procedure (see section Summarised cost related to the MRgFUS procedure and Table 16). There is in general uncertainty associated with estimation of costs, and comparisons across

countries and contexts. However, the provided cost for the procedure in Denmark does give some support that the cost calculated in this STA could be reasonable.

7.2.4 Accordance with other health economic evaluations

The submitter stated that there are few available cost-effectiveness studies that compare MRgFUS with no procedure for patients with medication-refractory essential tremor. They have identified these cost-effectiveness studies: Jameel 2022 (47) and Li 2019 (46). According to the submitter, Jameel 2022 has adapted the model by Li 2019, which is the same model/study as Health Quality Ontario (2018) (15). Se information about the studies and their results in Table 24.

The submitter also identified a cost-minimisation analysis by Igarashi and colleagues (71), and a cost-effectiveness study by Ravikumar and colleagues that compared MRgFUS with DBS (72). Since DBS was not used as comparator in this STA, we have not presented these studies.

Table 24. *Relevant cost-effectiveness studies on MRgFUS vs. no procedure in medication-refractory ET patients. The table is copied from the submission with some adjustments.*

Study, year, country (study conducted)	Type of analysis	Patient population (diagnosis, age, sex)	Incremental QALY benefit	Incremental costs	ICER
Jameel 2022 (47) UK	Decision tree combined with Markov cohort	Medication-refractory ET Starting age at 70 years 50% females	0.77 QALYs	£16,000	£20,851 per QALY
Li 2019 (46) Canada	Markov cohort model	Moderate to severe medically refractory ET Starting age 71 years 68% male	0.47 QALYs	$21,438	$45,817 per QALY

Abbreviations: *QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio*

Information on comparisons with DBS has been removed from the original table.

In Li 2019, the cost of the MRgFUS device and equipment was excluded since this was already in place in two centres in Ontario. If they would have included this cost, the ICER would have almost doubled, according to the authors.

7.3 Implications of the findings for practice

This STA demonstrates that unilateral MRgFUS is an effective and safe treatment option for patients with medication-refractory, moderate to severe ET. MRgFUS reduced hand tremor and disability, and these improvements can have huge impact for individual patients. In line with this, we found that MRgFUS probably improved the patients' quality of life. MRgFUS can also impact the patients' next of kin as these are also substantially affected by the disease.

Some patients with medication-refractory, moderate to severe ET are currently offered DBS in Norway. MRgFUS was not compared with DBS in this STA. The STA therefore suggest that MRgFUS may be offered to patients who are ineligible or unwilling to undergo DBS, but does not investigate whether (or not) MRgFUS is more effective than DBS. Our clinical experts explained that ET patients who are ineligible or unwilling to undergo DBS need new

treatment options, and agreed with the submitter that it was reasonable to investigate this population.

There are also organisational aspects that need to be considered before MRgFUS can be offered in Norway. Some of these are detailed in *Chapter 4: Organisational considerations*. Briefly, decision makers must decide how many locations that should offer MRgFUS in Norway. The submitter assumed that 100 ET patients will be treated with MRgFUS yearly and suggested that two locations may be appropriate. Implementation of MRgFUS would entail relatively high investment costs. One may consider only one location which would imply lower investment costs and a need for specially trained personnel in only one place. The submitter emphasised that the MRgFUS procedure requires a multidisciplinary team and skill acquisition. Training was not described, but the submitter indicated that 20 procedures were required for certification and that a learning curve of 50 procedures can be expected.

The treatment procedure lasts 3–4 hours which means that two patients may be treated per day. Hundred ET patients per year could thus be treated in 50 days (approximately one full treatment day per week). Decision makers should also consider changes in the need for MR capacity. Fifty full days of MR-scanning will be required for MRgFUS per year because the treatment is performed inside a MR-scanner. During these days, the MR scanner would not be available for other patients.

This STA investigated the effect of unilateral MRgFUS for ET. MRgFUS has also been suggested for other indications including Parkinson's disease and dystonia (73-75). Unilateral MRgFUS was recently approved by the U.S. Food and Drugs Administration for tremor-dominant Parkinson's disease (73). Our clinical experts expect that MRgFUS will be offered for new indications in the future. If this happens, the costs per MRgFUS procedure may be lowered because investment costs are divided on more procedures. The need for MRgFUS treatment capacity may also be increased. However, we emphasise that the clinical effect and costs of MRgFUS for ET found in this STA, do not necessarily apply for other indications. Separate analysis and evaluations are needed for other indications.

7.4 Need for further research

One RCT (Elias 2016) compared unilateral MRgFUS with sham for patients with medication-refractory, moderate to severe ET. The RCT reported effects for the two groups within a follow-up period of three months. There is a need for new RCTs with longer follow-up to investigate the duration of treatment effects (beyond three months). If solid evidence for the duration of treatment effects is provided, one could conduct a new health economic evaluation that would have less uncertainty related to these parameters.

Furthermore, all the included studies investigated relatively small patient cohorts (30–215 patients). New studies with large patient cohorts, that have the statistical power to detect possible rare occurring adverse events, are needed.

A list of ongoing studies is presented in Appendix 4. All the ongoing studies are single arm studies with relatively few planned or recruited patients (11–51 patients). None of the ongoing studies will thus address the issues raised above.

8. Conclusion

Unilateral MRgFUS appeared to be an effective and safe treatment option for patients with medication-refractory, moderate to severe ET. Unilateral MRgFUS reduced hand tremor and disability, and probably improved quality of life three months after the treatment. The treatment effects may persist substantially longer, but the long-term effects were associated with low certainty. Adverse events were common, but mostly mild and transient. Studies with larger patient cohorts are needed to identify or rule out possible adverse events that may occur rarely.

The cost-effectiveness analysis indicated that unilateral MRgFUS generates more QALYs, but at a higher cost than no procedure. The estimated ICER was approximately NOK 189,000 per QALY. There was uncertainty associated with the duration of the treatment effect, utilities, the actual cost of the MRgFUS procedure, and other parameters in the model.

Implementation of MRgFUS could entail budget impact of around NOK [redacted] million over five years, and implementation of two devices could entail budget impact of around NOK [redacted] million.

9. References

1. Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, et al. Consensus Statement on the classification of tremors. from the task force on tremor of the International Parkinson and Movement Disorder Society. Mov Disord 2018;33(1):75-87. DOI: 10.1002/mds.27121
2. Louis ED. Essential tremor: "Plus" or "Minus". Perhaps now is the time to adopt the term "the essential tremors". Parkinsonism Relat Disord 2018;56:111-2. DOI: 10.1016/j.parkreldis.2018.06.026
3. Flengsrud K, Toft M, Dietrichs E. [Essential tremor]. Tidsskr Nor Laegeforen 2019;139(8). DOI: 10.4045/tidsskr.18.0904
4. Norsk Helseinformatikk. Skjelvinger - essensiell tremor[lest 16.08.2024]. Tilgjengelig fra: https://nhi.no/sykdommer/hjernenervesystem/muskelrykninger/skjelvinger-essensiell-tremor
5. Espay AJ, Lang AE, Erro R, Merola A, Fasano A, Berardelli A, et al. Essential pitfalls in "essential" tremor. Mov Disord 2017;32(3):325-31. DOI: 10.1002/mds.26919
6. Song P, Zhang Y, Zha M, Yang Q, Ye X, Yi Q, et al. The global prevalence of essential tremor, with emphasis on age and sex: A meta-analysis. J Glob Health 2021;11:04028. DOI: 10.7189/jogh.11.04028
7. Louis ED, Ferreira JJ. How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. Mov Disord 2010;25(5):534-41. DOI: 10.1002/mds.22838
8. Clark LN, Louis ED. Challenges in essential tremor genetics. Rev Neurol (Paris) 2015;171(6-7):466-74. DOI: 10.1016/j.neurol.2015.02.015
9. Buijink AW, van der Stouwe AM, Broersma M, Sharifi S, Groot PF, Speelman JD, et al. Motor network disruption in essential tremor: a functional and effective connectivity study. Brain 2015;138(Pt 10):2934-47. DOI: 10.1093/brain/awv225
10. Hua SE, Lenz FA. Posture-related oscillations in human cerebellar thalamus in essential tremor are enabled by voluntary motor circuits. J Neurophysiol 2005;93(1):117-27. DOI: 10.1152/jn.00527.2004
11. Parras O, Dominguez P, Tomas-Biosca A, Guridi J. The role of tractography in the localisation of the Vim nucleus of the thalamus and the dentatorubrothalamic tract for the treatment of tremor. Neurologia (Engl Ed) 2022;37(8):691-9. DOI: 10.1016/j.nrleng.2019.09.008
12. Kvernmo N, Konglund AE, Reich MM, Roothans J, Pripp AH, Dietrichs E, et al. Deep Brain Stimulation for Arm Tremor: A Randomized Trial Comparing Two Targets. Ann Neurol 2022;91(5):585-601. DOI: 10.1002/ana.26317
13. Zesiewicz TA, Elble RJ, Louis ED, Gronseth GS, Ondo WG, Dewey RB, Jr., et al. Evidence-based guideline update: treatment of essential tremor: report of the Quality Standards subcommittee of the American Academy of Neurology. Neurology 2011;77(19):1752-5. DOI: 10.1212/WNL.0b013e318236f0fd
14. Romero JP, Benito-Leon J, Bermejo-Pareja F. The NEDICES Study: Recent Advances in the Understanding of the Epidemiology of Essential Tremor. Tremor Other Hyperkinet Mov (N Y) 2012;2. DOI: 10.7916/D8N58K4H
15. Health Quality O. Magnetic Resonance-Guided Focused Ultrasound Neurosurgery for Essential Tremor: A Health Technology Assessment. Ont Health Technol Assess Ser 2018;18(4):1-141.
16. Gassner LAF, R; Goetz, G. Transcranial magnetic resonance-guided high-intensity focused ultrasound treatment in patients with drug-resistant essential tremor. Austrian Institute for Health Technology Assessment GmbH; 2023. Tilgjengelig fra: https://eprints.aihta.at/1455/1/DSD_136.pdf
17. HTA syd. Fokuserad ultraljudsbehandling vid tremor. Lund: Region Skåne; 2023. Tilgjengelig fra: https://vardgivare.skane.se/kompetens-utveckling/sakkunniggrupper/hta-skane/#110365
18. Elias WJ, Lipsman N, Ondo WG, Ghanouni P, Kim YG, Lee W, et al. A Randomized Trial of Focused Ultrasound Thalamotomy for Essential Tremor. N Engl J Med 2016;375(8):730-9. DOI: 10.1056/NEJMoa1600159

19. Chang JW, Park CK, Lipsman N, Schwartz ML, Ghanouni P, Henderson JM, et al. A prospective trial of magnetic resonance-guided focused ultrasound thalamotomy for essential tremor: Results at the 2-year follow-up. Ann Neurol 2018;83(1):107-14. DOI: 10.1002/ana.25126
20. Halpern CH, Santini V, Lipsman N, Lozano AM, Schwartz ML, Shah BB, et al. Three-year follow-up of prospective trial of focused ultrasound thalamotomy for essential tremor. Neurology 2019;93(24):e2284-e93. DOI: 10.1212/WNL.0000000000008561
21. Cosgrove GR, Lipsman N, Lozano AM, Chang JW, Halpern C, Ghanouni P, et al. Magnetic resonance imaging-guided focused ultrasound thalamotomy for essential tremor: 5-year follow-up results. J Neurosurg 2023;138(4):1028-33. DOI: 10.3171/2022.6.JNS212483
22. Chang KW, Park YS, Chang JW. Skull Factors Affecting Outcomes of Magnetic Resonance-Guided Focused Ultrasound for Patients with Essential Tremor. Yonsei Med J 2019;60(8):768-73. DOI: 10.3349/ymj.2019.60.8.768
23. Meng Y, Solomon B, Boutet A, Llinas M, Scantlebury N, Huang Y, et al. Magnetic resonance-guided focused ultrasound thalamotomy for treatment of essential tremor: A 2-year outcome study. Mov Disord 2018;33(10):1647-50. DOI: 10.1002/mds.99
24. Abe K, Horisawa S, Yamaguchi T, Hori H, Yamada K, Kondo K, et al. Focused Ultrasound Thalamotomy for Refractory Essential Tremor: A Japanese Multicenter Single-Arm Study. Neurosurgery 2021;88(4):751-7. DOI: 10.1093/neuros/nyaa536
25. Arcadi A, Aviles-Olmos I, Gonzalez-Quarante LH, Gorospe A, Jimenez-Huete A, de la Corte MM, et al. Magnetic Resonance-Guided Focused Ultrasound (MRgFUS)-Thalamotomy for Essential Tremor: Lesion Location and Clinical Outcomes. Mov Disord 2024;39(6):1015-25. DOI: 10.1002/mds.29801
26. Gasca-Salas C, Guida P, Piredda R, Obeso I, Vela Desojo L, Martinez-Fernandez R, et al. Cognitive safety after unilateral magnetic resonance-guided focused ultrasound thalamotomy for essential tremor. J Neurol Neurosurg Psychiatry 2019;90(7):830-1. DOI: 10.1136/jnnp-2018-320129
27. Golfre Andreasi N, Braccia A, Levi V, Rinaldo S, Ghielmetti F, Cilia R, et al. The Optimal Targeting for Focused Ultrasound Thalamotomy Differs between Dystonic and Essential Tremor: A 12-Month Prospective Pilot Study. Mov Disord Clin Pract 2024;11(1):69-75. DOI: 10.1002/mdc3.13911
28. Lu H, Lin J, Xiong Y, Deng L, Wang X, Zhang D, et al. Assessing the impact of MR-guided focused ultrasound thalamotomy on brain activity and connectivity in patients with essential tremor. Neurosurg Focus 2022;53(6):E5. DOI: 10.3171/2022.9.FOCUS22228
29. Peters J, Maamary J, Kyle K, Olsen N, Jones L, Bolitho S, et al. Outcomes of Focused Ultrasound Thalamotomy in Tremor Syndromes. Mov Disord 2024;39(1):173-82. DOI: 10.1002/mds.29658
30. Purrer V, Borger V, Pohl E, Upadhyay N, Boecker H, Schmeel C, et al. Transcranial high-intensity Magnetic Resonance-guided focused ultrasound (tcMRgFUS) - safety and impacts on tremor severity and quality of life. Parkinsonism Relat Disord 2022;100:6-12. DOI: 10.1016/j.parkreldis.2022.05.017
31. Sinai A, Nassar M, Eran A, Constantinescu M, Zaaroor M, Sprecher E, et al. Magnetic resonance-guided focused ultrasound thalamotomy for essential tremor: a 5-year single-center experience. J Neurosurg 2020;133(2):417-24. DOI: 10.3171/2019.3.JNS19466
32. Zur G, Lesman-Segev OH, Schlesinger I, Goldsher D, Sinai A, Zaaroor M, et al. Tremor Relief and Structural Integrity after MRI-guided Focused US Thalamotomy in Tremor Disorders. Radiology 2020;294(3):676-85. DOI: 10.1148/radiol.2019191624
33. Blitz SE, Chua MMJ, Ng P, Segar DJ, Jha R, McDannold NJ, et al. Longitudinal MR imaging after unilateral MR-guided focused ultrasound thalamotomy: clinical and radiological correlation. Front Neurol 2023;14:1272425. DOI: 10.3389/fneur.2023.1272425
34. Hino S, Maki F, Yamaguchi T, Kaburagi M, Nakano M, Iwamuro H, et al. Effectiveness and safety of MR-guided focused ultrasound thalamotomy in patients with essential tremor and low skull density ratio: a study of 101 cases. J Neurosurg 2024;141(1):212-20. DOI: 10.3171/2023.11.JNS231799

35. Lak AM, Segar DJ, McDannold N, White PJ, Cosgrove GR. Magnetic Resonance Image Guided Focused Ultrasound Thalamotomy. A Single Center Experience With 160 Procedures. Front Neurol 2022;13:743649. DOI: 10.3389/fneur.2022.743649
36. Segar DJ, Lak AM, Lee S, Harary M, Chavakula V, Lauro P, et al. Lesion location and lesion creation affect outcomes after focused ultrasound thalamotomy. Brain 2021;144(10):3089-100. DOI: 10.1093/brain/awab176
37. Mueller JM, Chiu LT, Lynn F, Lewis RG, Patel S, Wodziak M, et al. Magnetic Resonance-Guided Focused Ultrasound without Anesthesiologist Support. Stereotact Funct Neurosurg 2024;102(3):169-78. DOI: 10.1159/000537695
38. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928. DOI: 10.1136/bmj.d5928
39. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898. DOI: 10.1136/bmj.l4898
40. Barker TH, Habibi N, Aromataris E, Stone JC, Leonardi-Bee J, Sears K, et al. The revised JBI critical appraisal tool for the assessment of risk of bias for quasi-experimental studies. JBI Evid Synth 2024;22(3):378-88. DOI: 10.11124/JBIES-23-00268
41. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017;358:j4008. DOI: 10.1136/bmj.j4008
42. RevMan Web (Review Manager). The Cochrane Collaboration. Tilgjengelig fra: https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman
43. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64(4):383-94. DOI: 10.1016/j.jclinepi.2010.04.026
44. Principles for priority setting in health care. Summary of a white paper on priority setting in the Norwegian health care sector. Oslo: Norwegian Ministry of Health and Care Services; 2017. Tilgjengelig fra: https://www.regjeringen.no/contentassets/439a420e01914a18b21f351143ccc6af/en-gb/pdfs/stm201520160034000engpdfs.pdf
45. Fahn S, Tolosa E, Marín C. Clinical Rating Scale for Tremor: Baltimore-Münich: Urban & Schwarzenberg; 1988.
46. Li C, Gajic-Veljanoski O, Schaink AK, Higgins C, Fasano A, Sikich N, et al. Cost-Effectiveness of Magnetic Resonance-Guided Focused Ultrasound for Essential Tremor. Mov Disord 2019;34(5):735-43. DOI: 10.1002/mds.27587
47. Jameel A, Meiwald A, Bain P, Patel N, Nandi D, Jones B, et al. The cost-effectiveness of unilateral magnetic resonance-guided focused ultrasound in comparison with unilateral deep brain stimulation for the treatment of medically refractory essential tremor in England. Br J Radiol 2022;95(1140):20220137. DOI: 10.1259/bjr.20220137
48. Jameel A, Gedroyc W, Nandi D, Jones B, Kirmi O, Molloy S, et al. Double lesion MRgFUS treatment of essential tremor targeting the thalamus and posterior sub-thalamic area: preliminary study with two year follow-up. Br J Neurosurg 2022;36(2):241-50. DOI: 10.1080/02688697.2021.1958150
49. Health Quality Ontario. Magnetic Resonance-Guided Focused Ultrasound Neurosurgery for Essential Tremor: A Health Technology Assessment. Ont Health Technol Assess Ser 2018;18(4):1-141.
50. Herceg M, Nagy F, Pál E, Janszky J, Késmárky I, Komoly S, et al. Pramipexole may be an effective treatment option in essential tremor. Clin Neuropharmacol 2012;35(2):73-6. DOI: 10.1097/WNF.0b013e31824687bf
51. NIPH. Guidelines for the submission of documentation for single technology assessments (STAs) of medical devices and diagnostic interventions [unpublished]. Oslo: Norwegian Institute of Public Health; 2021.
52. Szende A, Németh R. [Health-related quality of life of the Hungarian population]. Orv Hetil 2003;144(34):1667-74.
53. Matza LS, Deger KA, Vo P, Maniyar F, Goadsby PJ. Health state utilities associated with attributes of migraine preventive treatments based on patient and general population preferences. Quality of Life Research 2019;28:2359-72.

54. van Roijen L, Essink-Bot M-L, Koopmanschap MA, Michel BC, Rutten FF. Societal perspective on the burden of migraine in the Netherlands. Pharmacoeconomics 1995;7:170-9.
55. Price list [Prisliste]: Unilabs, [lest]. Tilgjengelig fra: https://unilabs.no/pasient/radiologi/prisliste
56. Salary [Lønn]: Statistics Norway, [lest 22 November]. Tilgjengelig fra: https://www.ssb.no/statbank/table/11418/
57. Unit cost database [Enhetskostnadsdatabase]Oslo: Norwegian Medical Products Agency [lest 22 November]. Tilgjengelig fra: https://www.dmp.no/en/public-funding-and-pricing/health-technology-assessments/medicines/submission-of-documentation-for-single-technology-assessment-of-pharmaceuticals/unit-cost-database
58. Salary and future prospects for radiographer [Lønn og fremtidsutsikter for Radiograf]: Keystone Education Group AB [lest 22 November]. Tilgjengelig fra: https://www.studentum.no/jobb-og-lonn/radiograf
59. Salary and future prospects for cleaning operator [Lønn og fremtidsutsikter for Renholdsoperatør]: Keystone Education Group AB [lest 22 November]. Tilgjengelig fra: https://www.studentum.no/jobb-og-lonn/renholdsoperator
60. Salary calculator [Lønnskalkulator]: Norges Farmaceutiske Forening [lest 22 November]. Tilgjengelig fra: https://www.farmaceutene.no/arbeidsrett-og-lonn/lonn/lonnskalkulator/
61. Price overview Sandvika Nevrosenter [Prisoversikt Sandvika Nevrosenter]: Sandvika Nevrosenter, [lest 22 November]. Tilgjengelig fra: https://sandvikanevrosenter.no/prisliste/
62. Norwegian Directorate of Health. Regulations for Activity-Based Financing 2023 [Regelverk for innsatsstyrt finansiering 2023]. Oslo: 2023. Regulation. Tilgjengelig fra: https://www.helsedirektoratet.no/tema/finansiering/innsatsstyrt-finansiering-og-drg-systemet/innsatsstyrt-finansiering-isf
63. Price list [Prisliste]: STERK, [lest 22 November]. Tilgjengelig fra: https://www.sterkhelse.no/prisliste/
64. Clinical expert input. 25 October 2024.
65. Resnick AS, Okun MS, Malapira T, Smith D, Vale FL, Sullivan K, et al. Sustained Medication Reduction Following Unilateral VIM Thalamic Stimulation for Essential Tremor. Tremor Other Hyperkinet Mov (N Y) 2012;2. DOI: 10.7916/d8zg6qz2
66. Net Monetary Benefit: York Health Economics Consortium [lest 6 December]. Tilgjengelig fra: https://yhec.co.uk/glossary/net-monetary-benefit/
67. Health Technology Assessment International. Patient participation: non-medicines HTA[lest 18.10.2024]. Tilgjengelig fra: https://healthtai.sharepoint.com/:w:/s/IGWebsiteContent/EaZ8DfVxtiFMrQvgvC0E7ewBZhzaBFjh0COBtt56_h_BFg?e=d5eEZ6
68. Essensiell Tremor-Foreningen Norge. Spørreundersøkelse om essensiell tremor i Norge[lest]. Tilgjengelig fra: https://essensielltremor.no/
69. Helse- og omsorgsdepartementet. Verdier i pasientens helsetjeneste: Melding om prioritering. 2016. Meld. St. 34 (2015–2016). Tilgjengelig fra: https://www.regjeringen.no/no/dokumenter/meld.-st.-34-20152016/id2502758/
70. Foreign Office at Oslo University Hospital. 17 September 2024.
71. Igarashi A, Tanaka M, Abe K, Richard L, Peirce V, Yamada K. Cost-minimisation model of magnetic resonance-guided focussed ultrasound therapy compared to unilateral deep brain stimulation for essential tremor treatment in Japan. PloS one 2019;14(7):e0219929.
72. Ravikumar VK, Parker JJ, Hornbeck TS, Santini VE, Pauly KB, Wintermark M, et al. Cost-effectiveness of focused ultrasound, radiosurgery, and DBS for essential tremor. Movement Disorders 2017;32(8):1165-73.
73. Eisenberg HM, Krishna V, Elias WJ, Cosgrove GR, Gandhi D, Aldrich CE, et al. MR-guided focused ultrasound pallidotomy for Parkinson's disease: safety and feasibility. J Neurosurg 2021;135(3):792-8. DOI: 10.3171/2020.6.JNS192773
74. Ko TH, Lee YH, Chan L, Tsai KW, Hong CT, Lo WL. Magnetic Resonance-Guided focused ultrasound surgery for Parkinson's disease: A mini-review and comparison between deep brain stimulation. Parkinsonism Relat Disord 2023;111:105431. DOI: 10.1016/j.parkreldis.2023.105431

75. Momin SMB, Aquilina K, Bulstrode H, Taira T, Kalia S, Natalwala A. MRI-Guided Focused Ultrasound for the Treatment of Dystonia: A Narrative Review. Cureus 2024;16(2):e54284. DOI: 10.7759/cureus.54284

Appendix 1: Progress log

Date	Milestone
19.06.2023	NIPH (Norwegian Institute of Public Health) is commissioned to perform an STA on MRgFUS for essential tremor and Parkinson's disease based on documentation from Insightec, the owner of the technology
08.09.2023	Initial meeting between Insightec and NIPH
11.12.2023	The responsibility for the STA is transferred to NOMA, as part of the reorganisation of the central health authorities in Norway
08.02.2024	NOMA asks "Nye metoder" to recruit clinical experts
01.03.2024	Clinical experts recruited and contacted
12.03.2024	Insightec informs that the documentation is delayed
18.03.2024	In initial meetings, Insightec claims that the evidence for Parkinson's disease is insufficient and asks to submit documentation only for essential tremor. The scope of the STA is changed to only concern essential tremor (Parkinson's disease is excluded).
29.04.2024	Insightec submits documentation
15.05.2024	NOMA informs Inisightec that the provided documentation has several shortcomings and offers Insightec to submit revised documentation
23.05.2024	Meeting between Insightec and NOMA to discuss shortcomings of the initial documentation and possible solutions for revised documentation
18.06.2024	Meeting between Insightec and NOMA in which Insightec suggest removing the comparison with deep brain stimulation (DBS)
19.06.2024	NOMA asks clinical experts whether it is appropriate to remove comparison with DBS. The clinical experts agree that this is appropriate because the relevant population is patients who are ineligible or unwilling to undergo DBS.
20.06.2024	NOMA notifies Insightec that DBS may be removed as comparator
17.07.2024	Insightec submits revised documentation
13.08.2024	NOMA formally accepts the revised documentation
31.08.2024	Patient representative recruited
20.12.2025	NOMA sends the report to Insightec for fact check, and check of confidential information
08.01.2025	NOMA receives feedback from Insightec
10.01.2025	NOMA submits the report to "Nye metoder"

Appendix 2: Literature search strategy

The submitter performed searches in Medline and Medline In-Process (PubMed), Embase (Ovid), Cochrane Central Register of Controlled Trials (CENTRAL), US National Library of Medicine Clinical Trials, and the WHO International Clinical Trials Registry Platform.

Medline and Medline In-Process (PubMed) (04/06/2024)

Search no.	Search terms	No. of articles
Population		
#1	"essential tremor"[Mesh] OR ((essential[tiab] OR familial[tiab] OR hereditary[tiab] OR heredofamilial[tiab] OR heredo-familial[tiab] OR juvenile[tiab] OR presenile[tiab] OR senile[tiab] OR benign[tiab] OR idiopathic[tiab] OR kinetic[tiab] OR action[tiab] OR postural[tiab] OR intention[tiab]) AND tremor*[tiab])	11,215
Intervention		
#2	Ultrasonic Therapy[Mesh] OR Ultrasonography, Interventional[Mesh] OR Thalamus / surgery[Mesh Subheading] OR Ventral Thalamic Nuclei / surgery[Mesh Subheading] OR "high intensity focused ultrasound ablation"[tiab] OR "focused ultrasound"[tiab] OR thalamotomy[tiab] OR "ventral intermediate nucleus"[tiab] OR cerebellothalamic[tiab] OR ExAblate[tiab] OR MRgFU*[tiab] OR MRgHIFU*[tiab] OR HIFU[tiab] OR USgHIFU[tiab] OR "posterior subthalamic area"[tiab] OR Insightec[tiab] OR "focused ultrasonograph*"[tiab] OR TcMRgFU*[tiab]	56,379
#3	#1 AND #2	1,153
#4	#1 AND #2 Filters: English	**1,076**

Embase (Ovid) (04/06/2024)

Search no.	Search terms	No. of articles
Population		
#1	exp "essential tremor"/ OR ((essential OR familial OR hereditary OR heredofamilial OR heredo-familial OR juvenile OR presenile OR senile OR benign OR idiopathic OR kinetic OR action OR postural OR intention).ti,ab. AND tremor*.ti,ab.)	19,423
Intervention		
#2	exp "Ultrasonic Therapy"/ OR ((thalam* AND (surg* or neurosurg* or ablat*)) or thalamotom*).ti,ab. OR exp thalamus ventral nucleus/ OR "high intensity focused ultrasound ablation".ti,ab. OR "focused ultrasound".ti,ab. OR thalamotomy.ti,ab. OR "ventral intermediate nucleus".ti,ab. OR cerebellothalamic.ti,ab. OR ExAblate.ti,ab. OR MRgFU*.ti,ab. OR MRgHIFU*.ti,ab. OR HIFU.tw. OR USgHIFU.ti,ab. OR "posterior subthalamic area".ti,ab. OR Insightec.ti,ab. OR "focused ultrasonograph*".ti,ab. OR TcMRgFU*.ti,ab. OR exablate.ti,ab. OR exp interventional ultrasonography/	50,428
#3	#1 AND #2	2,200
#4	limit 3 to (english language and "remove medline records")	**1,001**

Cochrane CENTRAL (04/06/2024)

Search no.	Search terms	No. of articles
Population		
#1	[mh "essential tremor"] OR ((essential:ti,ab OR familial:ti,ab OR hereditary:ti,ab OR heredofamilial:ti,ab OR heredo-familial:ti,ab OR juvenile:ti,ab OR presenile:ti,ab OR senile:ti,ab OR benign:ti,ab OR idiopathic:ti,ab OR kinetic:ti,ab OR action:ti,ab OR postural:ti,ab OR intention:ti,ab) AND tremor*:ti,ab)	1,096
Intervention		
#2	[mh "Ultrasonic Therapy"] OR [mh "Ultrasonography, Interventional"] OR [mh Thalamus] OR [mh "Ventral Thalamic Nuclei"] OR "high intensity focused ultrasound ablation":ti,ab OR "focused ultrasound":ti,ab OR thalamotomy:ti,ab OR "ventral intermediate nucleus":ti,ab OR cerebellothalamic:ti,ab OR ExAblate:ti,ab OR MRgFU*:ti,ab OR MRgHIFU*:ti,ab OR HIFU:ti,ab OR USgHIFU:ti,ab OR "posterior subthalamic area":ti,ab OR Insightec:ti,ab OR ("focused" NEXT ultrasonograph*):ti,ab OR TcMRgFU*:ti,ab	5,684
#3	#1 AND #2	116
#4	Limit 3 in Trials (from ICTRP and ClinialTrials.gov, excluding PubMed and Embase sources)	**21**

US National Library of Medicine Clinical Trials (07/06/2024)

Search no.	Search terms	No. of articles
Population		
#1	((essential OR familial OR hereditary OR heredofamilial OR heredo-familial OR juvenile OR presenile OR senile OR benign OR idiopathic OR kinetic OR action OR postural OR intention) AND tremor*)	250
Intervention		
#2	"high intensity focused ultrasound ablation" OR "focused ultrasound" OR thalamotomy OR "ventral intermediate nucleus" OR cerebellothalamic OR ExAblate OR MRgFU* OR MRgHIFU* OR HIFU OR USgHIFU OR "posterior subthalamic area" OR Insightec OR focused ultrasonograph* OR TcMRgFU*	585
#3	Limit 3 with Study Status	**44**

WHO International Clinical Trials Registry Platform (WHO ICTRP) (07/06/2024)

Search no.	Search terms	No. of articles
#1	((essential OR familial OR hereditary OR heredofamilial OR heredo-familial OR juvenile OR presenile OR senile OR benign OR idiopathic OR kinetic OR action OR postural OR intention) AND tremor*) AND ("high intensity focused ultrasound ablation" OR "focused ultrasound" OR thalamotomy OR "ventral intermediate nucleus" OR cerebellothalamic OR ExAblate OR MRgFU* OR MRgHIFU* OR HIFU OR USgHIFU OR "posterior subthalamic area" OR Insightec OR focused ultrasonograph* OR TcMRgFU*)	**51**

Appendix 3: NOMA's additional literature search

NOMA performed additional searches in US National Library of Medicine Clinical Trials (clinicaltrials.gov) and WHO International Clinical Trials Registry Platform (ICTRP).

US National Library of Medicine Clinical Trials (Clinicaltrials.gov):

Search date: 04.09.24

Search description: Searches performed in boxes for Condition and Intervention with the following search strings:

[Condition:] ((essential OR familial OR hereditary OR heredofamilial OR heredo-familial OR juvenile OR presenile OR senile OR benign OR idiopathic OR kinetic OR action OR postural OR intention) AND tremor)

[Intervention:] ("Ultrasonic Therapy" OR Ultrasonography OR "focused ultrasound" OR thalamotomy OR ExAblate OR MRgFU OR MRgHIFU OR HIFU OR USgHIFU OR Insightec OR TcMRgFU)

Number of hits: 41

WHO ICTRP:

Search date: 04.09.24

Search description: Searches performed in basic search with the following search string:

(((essential OR familial OR hereditary OR heredofamilial OR heredo-familial OR juvenile OR presenile OR senile OR benign OR idiopathic OR kinetic OR action OR actions OR postural OR intention OR intentions) AND (tremor OR tremors))) AND (("Ultrasonic Therapy" OR (Ultrasonography OR Ultrasonographic) OR "focused ultrasound" OR (thalamotomy OR thalamotomies) OR ExAblate OR MRgFU OR MRgHIFU OR HIFU OR USgHIFU OR Insightec OR TcMRgFU))

Number of hits: 41

Appendix 4: Ongoing studies

The ongoing studies were identified in searches conducted in the databases US National Library of Medicine Clinical Trials (clinicaltrials.gov) and WHO International Clinical Trials Registry Platform (ICTRP) and are listed below. According to the inclusion criteria, ongoing studies of unilateral MRgFUS were included. The submitter also included ongoing studies of bilateral MRgFUS because these studies may report results from the first procedure (unilateral).

Table 25. *Ongoing studies investigating the effect of MRgFUS for essential tremor*

Study ID and study title	Population *	Intervention and comparator	Outcomes and follow-up time	Start and expected completion, status
NCT05624385 MRgFUS Thalamotomy for Therapy-Resistant Tremor-related Disease with Low SDR Value	Patients with medication-refractory tremor-related diseases, and low skull density ratio n = 20	MRgFUS Single arm study (no comparator)	Effectiveness of MRgFUS Adverse events 2-year follow-up	February 2023 December 2025 Recruiting
NCT06331052 3-D Tractography Focused Ultrasound Ablation for Essential Tremor	Patients with moderate to severe medically refractory essential tremor n = 24	MRgFUS Single arm study (no comparator)	Absolute and relative change in tremor Adverse events 3-month follow-up	March 2024 February 2028 Recruiting
NCT04720469 A Second Magnetic Resonance Guided Focused Ultrasound Thalamotomy for Essential Tremor	Patients with medically refractory essential tremor n = 11	MRgFUS Single arm study (no comparator)	Change in tremor score Change in quality of life Adverse events 12-week follow-up	October 2020 March 2024 Completed
NCT04501484 Bilateral Essential Tremor Treatment with FUS BEST-FUS	Patients with essential tremor n = 10+40	MRgFUS Single arm study (no comparator)	Patient-based utility Change in quality of life Adverse events 12-36 months follow-up	July 2020 December 2025 Active not recruiting
NCT04112381 Bilateral Treatment of Medication-refractory Essential Tremor	Patients with bilateral medically refractory essential tremor n = 51	MRgFUS Single arm study (no comparator)	Adverse events 3-month follow-up	June 2020 June 2023 Active not recruiting
NCT03465761 Staged Bilateral Exablate Treatment of Medication-refractory Essential Tremor	Patients with bilateral medically refractory essential tremor n = 30	MRgFUS Single arm study (no comparator)	Tremor score Adverse events 12-month follow-up	January 2019 December 2023 Recruiting

* n refers to number of planned or actual recruited patients

Appendix 5: Risk of bias in non-randomised studies and systematic reviews

Table 26. *Risk of bias in the included prospective non-randomised studies as assessed by the Joanna Briggs Institute Checklist for Quasi-Experimental Studies checklist (40). The table has been copied from the submitted documentation.*

	Question	1	2	3	4	5	6	7	8	9
Study	**Outcome**									
Abe 2021	Overall	Y	N	Y	N/A	-	-	-	-	-
	Tremor outcomes	-	-	-	-	Y	N/A	Y	Y	Y
	QoL	-	-	-	-	Y	N/A	Y	Y	Y
Arcadi 2024	Overall	Y	N	Y	N/A	-	-	-	-	-
	Tremor outcomes	-	-	-	-	Y	N/A	Y	Y	Y
	Safety	-	-	-	-	Y	N/A	Unclear	Y	Y
Chang 2019	Overall	Y	N	Y	N/A	-	-	-	-	-
	Tremor outcomes	-	-	-	-	Y	N/A	Y	Unclear	Y
Gasca-Salas 2019	Overall	Y	N	Y	N/A	-	-	-	-	-
	Tremor outcomes	-	-	-	-	Y	N/A	Y	N	Y
Golfre Andreasi 2024	Overall	Y	N	Y	N/A	-	-	-	-	-
	Tremor outcomes	-	-	-	-	Y	N/A	Y	Y	Y
	Safety	-	-	-	-	Y	N/A	Unclear	Y	Y
Lu 2022	Overall	Y	N	Y	N/A	-	-	-	-	-
	Tremor outcomes	-	-	-	-	Y	N/A	Y	Y	Y
Meng 2018	Overall	Y	N	Y	N/A	-	-	-	-	-
	Tremor outcomes	-	-	-	-	Y	N/A	Y	Y	Y
	Safety	-	-	-	-	Y	N/A	Unclear	Y	Y
Peters 2024	Overall	Y	N	Y	N/A	-	-	-	-	-
	Tremor outcomes	-	-	-	-	Y	N/A	Y	Y	Y
	QoL	-	-	-	-	Y	N/A	Y	Y	Y
	Safety	-	-	-	-	Y	N/A	Y	Y	Y
Purrer 2022	Overall	Y	N	Y	N/A	-	-	-	-	-
	Tremor outcomes	-	-	-	-	Y	N/A	Y	Y	Y
	QoL	-	-	-	-	Y	N/A	Y	Y	Y
	Safety	-	-	-	-	Y	N/A	Y	Y	Y
Sinai 2019	Overall	Y	N	Y	N/A	-	-	-	-	-
	Tremor outcomes	-	-	-	-	Y	N/A	Y	N	Y
	QoL	-	-	-	-	Y	N/A	Y	N	Y
	Safety	-	-	-	-	Y	N/A	Y	N	Y
Zur 2020	Overall	Y	N	Y	N/A	-	-	-	-	-
	Tremor outcomes	-	-	-	-	Y	N/A	Y	Y	Y
	QoL	-	-	-	-	Y	N/A	Y	Y	Y

The questions for the JBI critical appraisal tool for quasi-experimental studies are presented below:
1 - It is clear in the study what is the "cause" and what is the "effect" (i.e., there is no confusion about which variable comes first)?
2 - Was there a control group?
3 - Were participants included in any comparisons similar?
4 - Were the participants included in any comparisons receiving similar treatment/care other than the exposure or intervention of interest?
5 - Were there multiple measurements of the outcome, both pre- and post-intervention/exposure?
6 - Were the outcomes of participants included in any comparisons measured in the same way?
7 - Were outcomes measured in a reliable way?
8 - Was follow-up complete, and if not, were differences between groups in terms of their follow-up adequately described and analysed?
9 - Was appropriate statistical analysis used?

Table 27. *Risk of bias in the included retrospective non-randomised studies as assessed by the Joanna Briggs Institute Checklist for Quasi-Experimental Studies checklist (40). The table has been copied from the submitted documentation.*

	Question	1	2	3	4	5	6	7	8	9
Study	**Outcome**									
Blitz 2023	Overall	Y	N	Y	N/A	-	-	-	-	-
	Tremor outcomes	-	-	-	-	Y	N/A	Y	N	Unclear
	Adverse events	-	-	-	-	N	N/A	Y	N	Unclear
Hino 2024	Overall	Y	N	Y	N/A	-	-	-	-	-
	Tremor outcomes	-	-	-	-	Y	N/A	Y	Y	Y
	Adverse events	-	-	-	-	N	N/A	Y	Unclear	Unclear
Lak 2022	Overall	Y	N	Y	N/A	-	-	-	-	-
	Tremor outcomes					Y	N/A	Y	N	Y
Mueller 2024	Overall	Y	N	Y	N/A	-	-	-	-	-
	Tremor outcomes	-	-	-	-	Y	N/A	Y	N	Y
	Adverse events	-	-	-	-	N	N/A	Y	N	Unclear
Segar 2021	Overall	Y	N	Y	N/A	-	-	-	-	-
	Tremor outcomes	-	-	-	-	Y	N/A	Y	Unclear	Y
	Adverse events *	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

* No discrete data on adverse events for patients with essential tremors

The questions for the JBI critical appraisal tool for quasi-experimental studies are presented below:
1 - It is clear in the study what is the "cause" and what is the "effect" (i.e., there is no confusion about which variable comes first)?
2 - Was there a control group?
3 - Were participants included in any comparisons similar?
4 - Were the participants included in any comparisons receiving similar treatment/care other than the exposure or intervention of interest?
5 - Were there multiple measurements of the outcome, both pre- and post-intervention/exposure?
6 - Were the outcomes of participants included in any comparisons measured in the same way?
7 - Were outcomes measured in a reliable way?
8 - Was follow-up complete, and if not, were differences between groups in terms of their follow-up adequately described and analysed?
9 - Was appropriate statistical analysis used?

Table 28. *Methodological quality in the included systematic reviews as assessed by AMSTAR 2 (41). The table is reproduced from the submitted documentation. Critical questions are shown in red.*

AMSTAR-2 items	Agrawal 2021	Miller 2022
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review, and did the report justify any significant deviations from the protocol?	No	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No	No
4. Did the review authors use a comprehensive literature search strategy?	Yes	No
5. Did the review authors perform study selection in duplicate?	Yes	Yes
6. Did the review authors perform data extraction in duplicate?	Yes	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	No
8. Did the review authors describe the included studies in adequate detail?	Yes	Partial yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	No
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	No
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes	No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Yes
15. If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	No
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Yes
Overall assessment of quality	**Critically low**	**Critically low**

Appendix 6: Relative effect in individual non-randomised studies

Table 29. *Reduction in hand tremor in non-randomised before-and-after studies*

Study	Reduction in hand tremor score *						
	3 m	6 m	12 m	24 m	36 m	48 m	60 m
Elias 2016 **	51.1% n = 56	47.2% n = 56	54.7% n = 70	56.2% n = 50	52.1% n = 52	49.5% n = 45	40.4% n = 40
Abe 2021	56.5% n = 35		56.4% n = 35				
Arcadi 2024	77.8% n =102	72.4% n = 78					
Gasca-Salas 2019			63.0% n = 27				
Golfre Andreasi 2024			53.3% n = 35				
Lu 2022		74.4% n = 30					
Peters 2024	63.0% n = 19	61.6% n = 16	58.3% n = 17	61.1% n = 13	59.2% n = 6		
Purrer 2022		70.8% n = 37	67.7% n = 37				
Sinai 2019		84.2% n = 31	78.9% n = 24	78.9% n = 15	81.6% n = 10	73.7% n = 6	84.2% n = 2
Zur 2019		79.0% n = 20					
Blitz 2023	n.a.		n.a.				
Hino 2024	63.3% n =101						
Lak 2022	82.3% n =110		80.5% n =101	74.3% n = 49			
Mueller 2024	83.8% n = 92						
Weighted average	72.1% n =515	68.4% n =268	66.2% n =346	66.4% n =127	57.1% n = 68	52.3% n = 51	42% n = 42

***** Hand tremor score was assessed by Clinical Rating Scale for Tremor part A and B (CRST A+B), Fahn-Tolosa-Marin Rating Scale (FTM), or Tremor Research Group Essential Tremor Rating Scale (TETRAS). Reduction in hand tremor refers to % reduction in hand tremor score as compared to baseline scores

****** Results from the population that were originally randomised to MRgFUS are shown for 3 and 6 months, and results from the entire population is shown for 12, 24, 36 48 and 60 months (the non-randomised study extension phase)

Abbreviations: m, months; n, number of patients; n.a., not available

Table 30. *Reduction in disability score in non-randomised before-and-after studies*

Study	Reduction in disability score *						
	3 m	6 m	12 m	24 m	36 m	48 m	60 m
Elias 2016 **	62.8% n = 56		67.4% n = 70	60.1% n = 50	56.1% n = 52	49.0% n = 45	44.5% n = 40
Abe 2021	60.0% n = 35		57.8% n = 35				
Arcadi 2024	82.5% n =102	79.7% n = 78					
Golfre Andreasi 2024			53.3% n = 35				
Lu 2022		77.4% n = 30					
Purrer 2022		69.6% n = 37	69.6% n = 37				
Hino 2024	64.1% n =101						
Weighted average	67.7% n =294	76.6% n =145	62.8% n =142	60.1% n =50	56.1% n =52	49.0% n = 45	44.5% n = 40

***** Disability score was assessed by Clinical Rating Scale for Tremor part C. Reduction in disability score refers to % reduction in disability score as compared to baseline scores.

****** Results from the population that were originally randomised to MRgFUS are shown for 3 months, and results from the entire population is shown for 12, 24, 36 48 and 60 months (the non-randomised study extension phase)

Abbreviations: m, months; n, number of patients

Table 31. *Improvement in quality of life in non-randomised before-and-after studies*

Study	Improvement in quality of life *						
	3 m	6 m	12 m	24 m	36 m	48 m	60 m
Elias 2016 **	45.7% n = 56		53.5% n = 70	41.9% n = 50	39.5% n = 52	34.9% n = 45	30.2% n = 40
Abe 2021	42.9% n = 35		46.3% n = 35				
Peters 2024	74.2% n = 19	67.8% n = 16	59.4% n = 17	49.8% n = 13	46.8% n = 6		
Purrer 2022		52.1% n = 37	50.3% n = 37				
Sinai 2019		80.7% n = 31	66.3% n = 24	63.9% n = 15	62.7% n = 10	65.1% n = 6	73.5% n = 2
Zur 2019		71.6% n = 20					
Weighted average	49.7% n =110	67.7% n =104	53.7% n =183	47.4% n =78	43.6% n = 68	38.5% n = 51	32.3% n = 42

***** Quality of life was assessed by the Quality of Life in Essential Tremor questionary (QUEST). Improvement in quality of life refers to % improvement in QUEST as compared to baseline scores.

****** Results from the population that were originally randomised to MRgFUS are shown for 3 months, and results from the entire population is shown for 12, 24, 36 48 and 60 months (the non-randomised study extension phase)

Abbreviations: m, months; n, number of patients

Appendix 7: Age-adjustment of utility weights

Table 32. *Overview of age-adjustment of utility weights from 70 years*

HRQoL - age adjustment index					
70.0	Insert the baseline age in the model			Example HSUV:	0.811
Age	HRQoL for the general population	Adjustment index		Without age adjustment	With age adjustment
70	0.811312	1.000		0.811	0.811000
71	0.808333	0.996		0.811	0.808023
72	0.808333	0.996		0.811	0.808023
73	0.808333	0.996		0.811	0.808023
74	0.808333	0.996		0.811	0.808023
75	0.808333	0.996		0.811	0.808023
76	0.808333	0.996		0.811	0.808023
77	0.808333	0.996		0.811	0.808023
78	0.808333	0.996		0.811	0.808023
79	0.808333	0.996		0.811	0.808023
80	0.808333	0.996		0.811	0.808023
81	0.730000	0.900		0.811	0.729720
82	0.730000	0.900		0.811	0.729720
83	0.730000	0.900		0.811	0.729720
84	0.730000	0.900		0.811	0.729720
85	0.730000	0.900		0.811	0.729720
86	0.730000	0.900		0.811	0.729720
87	0.730000	0.900		0.811	0.729720
88	0.730000	0.900		0.811	0.729720
89	0.730000	0.900		0.811	0.729720
90	0.730000	0.900		0.811	0.729720
91	0.730000	0.900		0.811	0.729720
92	0.730000	0.900		0.811	0.729720
93	0.730000	0.900		0.811	0.729720
94	0.730000	0.900		0.811	0.729720
95	0.730000	0.900		0.811	0.729720
96	0.730000	0.900		0.811	0.729720
97	0.730000	0.900		0.811	0.729720
98	0.730000	0.900		0.811	0.729720
99	0.730000	0.900		0.811	0.729720
100	0.730000	0.900		0.811	0.729720

101	0.730000	0.900		0.811	0.729720
102	0.730000	0.900		0.811	0.729720
103	0.730000	0.900		0.811	0.729720
104	0.730000	0.900		0.811	0.729720
105	0.730000	0.900		0.811	0.729720
106	0.730000	0.900		0.811	0.729720

Appendix 8: Costs and resource use

MRgFUS costs and resource use

Table 33. *MRgFUS costs and resource use: Pre-procedure – 1–2 months prior to surgery*

	Unit cost	No of unit.	Used in model	Time in minutes	Used in model	Total cost
Scans						
CT scan	3290	1	1			3290
MRI scan	3890	1	1			3890
Assessment tests (fit for procedure)						
Specialist nurse	585	1	1	30	30	292
Anaesthetist consultation	822	1	1	15		822
Neurosurgeon consultation	3266	1	1	60		3266

Table 34. *MRgFUS costs and resource use: Pre-procedure – at the hospital*

	Unit cost	No of unit.	Used in model	Time in minutes	Used in model	Total cost
Admission and routine tests						
Administrative staff	374	1	1	30	30	187
Nurse	546	1	1	60	60	546
Blood test	141	1	1			141
Neurosurgeon	993	1	1	60	60	993
Radiologist or neuroradiologist	993	1	1	60	60	993
Average total of pre-procedure costs						**14422**

Table 35. *MRgFUS costs and resource use: Peri-procedure*

	Unit cost	No of unit.	Used in model	Time in minutes	Used in model	Total cost
Patient preparation (shaving)						
Nurse	546	1	1	30	30	273
System testing in the MR room						
MR technician	566	1	1	45	45	425
Physicist	566	1	1	45	45	425
Prep in the MR area (frame placement, IV, and monitoring)						
Nurse	546	1	1	60	60	546

Neurosurgeon	993	1	1	60	60	993
Neurologist	993	1	1	30	30	497
MR technician	566	1	1	60	60	566
Medication						
Antiemetics	5	36	36			176
Average total of peri-procedure costs (except procedure)					**3900**	

Table 36. *MRgFUS costs and resource use - procedure*

	Unit cost	No of unit.	Used in model	Time in minutes	Used in model	Total cost
Procedure						
Neurosurgeon	993	1	1	120	120	1 987
Neurologist	993	1	1	120	120	1 987
MRI technician	566	1	1	120	120	1 132
Neuroradiologist	993	1	1	120	120	1 987
Operating department practitioner (ODP)	330	1	1	120		6
Nurse	546	1	1	120	120	1 092
Antiemetics	5	4	4			20
Painkiller (Paracetamol)	0	1 000	1 000			250
Stretcher-bearer	317	1	1	20	20	106
Immediate post-treatment						
Cleaning solution	6	1	1			6
Nurse	546	1	1	60	60	546
Neurosurgeon	993	1	1	60	60	993
Neurologist	993	1	1	60	60	993
MR technician	566	1	1	60	60	566
MR-scanner use per case	3890	1	1	-	1	3890

Table 37. *Calculation of device cost per procedure*

Element for calculation	Value
Purchase value	NOK [redacted]
End of lifetime value	0
Amortisation periode (years)	10
Rate	4%
Cost per year	-NOK [redacted]
Cases per year	50
Cost per procedure with incl. amortisation	[redacted]

Per procedure cost with 15 % overhead cost	**NOK** [redacted]

Table 38. *MRgFUS costs and resource use: Post-procedure*

	Unit cost	No of unit.	Used in model	Time in minutes	Used in model	Total cost
MR technician	566	1	1	45	45	425
Neuroradiologist	993	1	1	45	45	745
Neurologist	993	1	1	60	60	993
Pharmacist	558	1	1	15	15	140
Physiotherapist	800	0	0	15		200
Nurse	546	1	1	30	30	273

Table 39. *Post procedure: length of stay*

	Unit cost	No of unit.	Used in model	Total cost
Stay in standard ward	21013	2	2	42026
MRI	3890	1	1	3890
Average post-procedure: recovery and patient discharge costs				**27678**

Table 40. *Follow-up costs*

Element	Unit cost	No of unit.	Total cost
1 week phone call			
Non-face to face neurology consultation	1950	1	1950
1 Month follow up			
Face to face neurology consultation	4130	1	4130
12 Month follow up			
Face to face neurology consultation	4130	1	4130
MRI	3890	1	3890
Annual follow up (year 2+)			
Face to face neurology consultation	4130	1	4130
Average follow up costs (1 year)			**14100**
Average follow up costs (2+ year)			**4130**

Ongoing medication costs

Table 41. *Ongoing medication cost*

	Cost per day	Proportion	Used in model	Total annual cost
MRgFUS				
Propranolol	NOK 15.05	50 %	50 %	NOK 2,748
Primidone	NOK 0.17			NOK -
Topiramate	NOK 33.34			NOK -
Alprazolam	NOK 4.47			NOK -
Total				NOK 2,748
No procedure				
	Cost per day	Proportion	Used in model	Total annual cost
Propranolol	NOK 15.05	75 %	75 %	NOK 4,122
Primidone	NOK 0.17			
Topiramate	NOK 33.34			
Alprazolam	NOK 4.47			
Total				NOK 4,122

Appendix 9: Input parameters in the one-way sensitivity analyses

Table 42. *Input parameters for the one-way sensitivity analysis copied from the submitted model, but with some adaptation*

Base case outcome	**412779**	**Low value**		**High value**	
Parameter	**Base case value**	**Value**	**NMB (NOK)**	**Value**	**NMB (NOK)**
MRgFUS - Proportion of patients with a mild-to-moderate improvement	42.9%	36.6%	523506	49.3%	478090
MRgFUS - Proportion of patients with an unsuccessful procedure	8.9%	7.6%	512587	10.2%	489486
MRgFUS - Annual probability of reoperation after recurrence	5.0%	4.3%	500680	5.8%	501393
Selected comparator - Proportion of patients with a mild-to-moderate improvement	42.9%	36.5%	501036	49.3%	501036
Selected comparator - Proportion of patients with an unsuccessful procedure	8.9%	7.6%	501036	10.2%	501036
Selected comparator - Annual probability of reoperation after recurrence	5.0%	4.3%	501036	5.8%	501036
MRgFUS - Probability of tremor recurrence	1.4%	1.2%	501036	1.6%	501036
MRgFUS - Marked improved tremor → Mild-to-moderate improved tremor	7.7%	6.5%	420865	8.9%	581142
MRgFUS - Marked improved tremor → Tremor recurrence (with reoperation)	0.0%	0.0%	501027	0.0%	501045
MRgFUS - Marked improved tremor → Tremor recurrence (without reoperation)	1.4%	1.2%	489284	1.6%	512785
MRgFUS - Mild-to-moderate improved tremor → Tremor recurrence (with reoperation)	0,0%	0,0%	501022	0,0%	501051
MRgFUS - Mild-to-moderate improved tremor → Tremor recurrence (without reoperation)	1.4%	1.2%	481958	1.6%	520106
MRgFUS - Mild-to-moderate improved tremor (post reop) → Tremor recurrence (without reoperation)	1.4%	1.2%	501035	1.6%	501038
MRgFUS - Marked improved tremor (post re-op) → Mild-to-moderate improved tremor	7.7%	6.5%	501036	8.9%	501037
MRgFUS - Marked improved tremor (post re-op) → Tremor recurrence (without reoperation)	1.4%	1.2%	501036	1.6%	501036
Selected comparator - Probability of tremor recurrence	1.4%	1.2%	501036	1.6%	501036
Selected comparator - Marked improved tremor → Mild-to-moderate improved tremor	9.2%	7.8%	501036	10.6%	501036
Selected comparator - Marked improved tremor → Tremor recurrence (with reoperation)	0.1%	0.1%	501036	0.1%	501036
Selected comparator - Marked improved tremor → Tremor recurrence (without reoperation)	1.3%	1.1%	501036	1.5%	501036
Selected comparator - Mild-to-moderate improved tremor → Tremor recurrence (with reoperation)	0.1%	0.1%	501036	0.1%	501036
Selected comparator - Mild-to-moderate improved tremor → Tremor recurrence (without reoperation)	1.3%	1.1%	501036	1.5%	501036
Selected comparator - Mild-to-moderate improved tremor (post reop) → Tremor recurrence (without reoperation)	1.4%	1.2%	501036	1.6%	501036
Selected comparator - Marked improved tremor (post re-op) → Mild-to-moderate improved tremor	9.2%	7.8%	501036	10.6%	501036
Selected comparator - Marked improved tremor (post re-op) → Tremor recurrence (without reoperation)	1.4%	1.2%	501036	1.6%	501036
MRgFUS - Probability of gait disturbance (per procedure)	27.0%	23.0%	501259	31.1%	500813

MRgFUS - Probability of paraesthesia or numbness (per procedure)	24.0%	20.4%	501263	27.6%	500810
MRgFUS - Probability of speech problem (per procedure)	4.0%	3.4%	501076	4.6%	500997
MRgFUS - Probability of headache (per procedure)	14.0%	11.9%	501217	16.1%	500856
MRgFUS - Probability of long-term gait disturbance (per procedure)	9.0%	7.7%	501525	10.4%	500548
MRgFUS - Probability of long-term paraesthesia or numbness (per procedure)	14.0%	11.9%	501933	16.1%	500140
MRgFUS - Duration of gait disturbance (years)	0.23	0.20	501068	0.27	501005
MRgFUS - Duration of paraesthesia or numbness (years)	0.36	0.30	501068	0.41	501004
MRgFUS - Duration of speech problem (years)	0.50	0.43	501051	0.58	501022
MRgFUS - Duration of headache (years)	0.15	0.13	501130	0.17	500943
MRgFUS - Duration of long-term gait disturbance (years)	50.00	43	501036	58	501036
MRgFUS - Duration of long-term paraesthesia or numbness (years)	50.00	43	501036	58	501036
MRgFUS - Pre-procedure costs (1 - 2- months prior to surgery)	14422	12258	503209	16585	498863
MRgFUS - Peri-procedure costs (day of surgery exc. procedure)	3900	3315	501624	4485	500449
MRgFUS - Procedure costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MRgFUS - Post-procedure: recovery and patient discharge	27678	23526	505207	31830	496866
MRgFUS - Follow up costs (year 1)	14100	11985	503161	16215	498912
MRgFUS - Follow up costs (year 2+)	4130	3511	507008	4750	495065
MRgFUS - Maintenance costs per case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MRgFUS - Annual ongoing medication costs	7591	6452	513150	8729	488922
Utility - Marked improved tremor	0.91	0.77	286807	1.00	642286
Utility - Mild-to-moderate improved tremor	0.80	0.68	153516	0.91	819597
Utility - Baseline tremor	0.69	0.59	963211	0.79	38862
Utility - Motor disturbance	0.77	0.66	497413	0.89	504660
Utility - Paraesthesia	0.77	0.66	496103	0.89	505970
Utility - Headache	0.77	0.65	499833	0.89	502240
Utility - Speech problem	0.77	0.50	498328	0.89	502187
Utility - Motor disturbance	0.77	0.66	463255	0.89	538817
Utility - Paraesthesia	0.77	0.66	443422	0.89	558651
Annual case load (MRgFUS)	50.00	42.50	501036	57.50	501036
No procedure - Annual consultation cost	8260	7021	487854	9499	514219
No procedure - Annual ongoing medication costs	0	0	501036	0	501036

Appendix 10: Probabilistic sensitivity analyses

Probabilistic sensitivity analysis

The submitter employed 1,000 simulations to generate probabilistic results, which encompass the uncertainties associated with multiple parameters in the cost-effectiveness model. The probability distribution functions for input parameters were defined using standard distributional forms: Dirichlet distribution (a distribution of categorical variables) was used for the proportion of patients with “marked improvement”, “mild-to-moderate improvement”, and “unsuccessful procedure”. Beta distribution was used for the probability of tremor recurrence, probability of reoperation after recurrence, the probability of transitioning from health state “marked improvement” to “mild-to-moderate improvement”, and utility decrements. A fixed distribution was used for the probability of staying in the health state marked improvement. Gamma distribution was used for costs.

To illustrate the results, a scatterplot is presented, presenting all the ICERs generated in the probabilistic sensitivity analyses. Additionally, cost-effectiveness acceptability curves were provided to illustrate the probability of an intervention being deemed optimal across different willingness-to-pay thresholds.

The results of the probabilistic sensitivity analyses are presented in Figure 17. The cost-effectiveness acceptability curve is presented in Figure 18.

The submitted PSA shows that MRgFUS has a likelihood of 100% of being cost effective at a WTP of NOK 500,000.

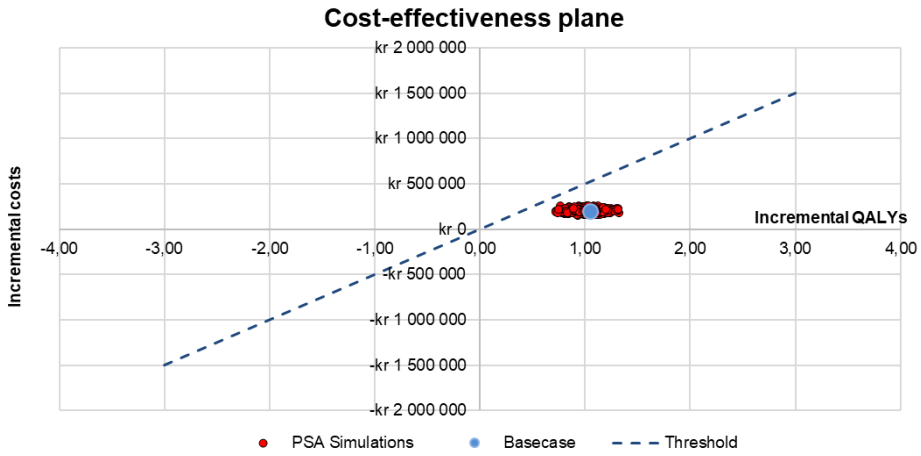

Figure 17. *Scatterplot of the PSA of NOMA’s base case analyses*

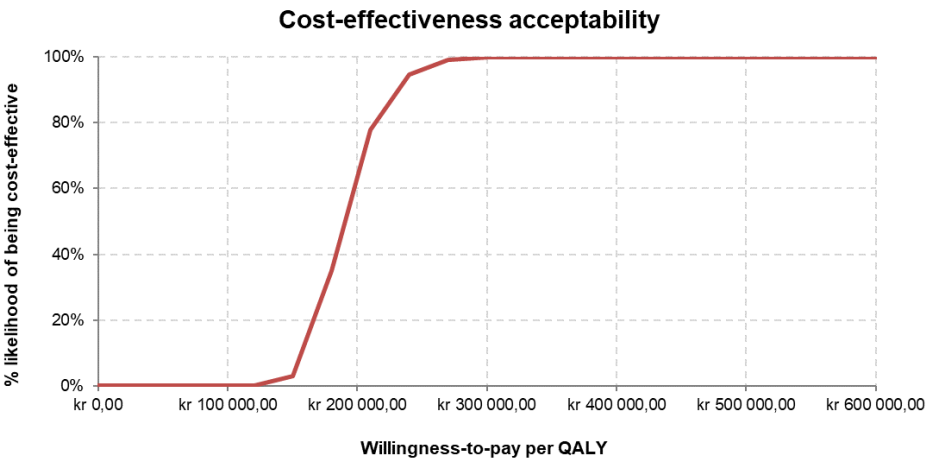

Figure 18. *Cost effectiveness acceptability curve*

Appendix 11: Inputs in the budget impact analyses

Inputs for the BIA with one device implemented

Number of MRgFUS devices installed

	Number	User Defined	Used in model
Devices in place before year 1	0	0	0
New devices year 1 to 5	1	1	1

Annual costs used in BIM (NOK)

Average annual cost per patient (overall population)	Year 1	Year 2	Year 3	Year 4	Year 5
MRgFUS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MRgFUS device (one off cost)	[redacted]	-	-	-	-
MRgFUS maintenance (once per year except first year)	-	[redacted]	[redacted]	[redacted]	[redacted]
No procedure	12,382	12,065	11,811	11,521	11,200

Inputs for the BIA with two devices implemented

Number of MRgFUS devices installed

	Number	User Defined	Used in model
Devices in place before year 1	0	0	0
New devices year 1 to 5	2	2	2

Annual costs used in BIM (NOK)

Average annual cost per patient (overall population)	Year 1	Year 2	Year 3	Year 4	Year 5
MRgFUS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MRgFUS device (one off cost)	[redacted]	-	-	-	-
MRgFUS maintenance (once per year except first year)	-	[redacted]	[redacted]	[redacted]	[redacted]
No procedure	12,382	12,065	11,811	11,521	11,200