Molina Clinical Policy
Magnetic Resonance Guided Focused Ultrasound (MRgFUS) for Essential Tremor: Policy No. 312

Last Approval: 2/8/2023
Next Review Due By: February 2024

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

Essential tremor (ET) is defined by the Tremor Task Force of the International Parkinson's and Movement Disorders Society (IPMDS) as an isolated tremor syndrome involving both upper limbs during action for a minimum time frame of 3 years, with or without tremor in other body segments (IPMDS, 2018). The condition is characterized by bilateral, symmetric, postural tremor in the hands and forearms, with or without kinetic tremor, in the absence of abnormal posturing or task specificity. Lower extremities, the head, and voice can also be affected. Symptoms can be barely noticeable or severe and disabling. Approximately 7 to 10 million people in the United States are affected – prevalence of ET ranges from 0.4% to 4.6% making it one of the most prevalent adult-onset movement disorders. Incidence of ET increases with age – the average age of onset is between the mid-to-late 40s. (Zesiewicz et al., 2017).

No signs of other neurologic disease such as dystonia, ataxia, or parkinsonism are allowed to be designated as ET (IPMDS, 2018). The underlying etiology of ET is unclear, but the disorder is considered to have a strong genetic component with family history in roughly 50% of cases and in 90% concordance in monozygotic twins (Agarwal and Biagioni, 2022). ET is a progressive condition with no known cure and can cause significant distress and impede functionality. Diagnosis is currently based on the clinical features and family history. Laboratory and imaging studies are usually not required and there is no biomarker for ET. There is no known definitive cure for ET and goals of treatment include reduction in tremor severity and disability while improving QOL (AANI, 2017). Pharmacotherapy, neurostimulation (with deep brain stimulation), and ablative therapies (with radiofrequency, stereotactic radiosurgery, or targeted ultrasound) are available treatment options, although each has limits. Pharmacotherapy is the first-line treatment for ET, with propranolol (the only FDA approved drug for ET) and primidone considered first-line medications. Second-line therapy commonly used in clinical practice typically includes benzodiazepines (clonazepam, alprazolam), anticonvulsants (gabapentin, pregabalin, topiramate), beta-blockers (atenolol and metoprolol) and zonisamide (Agarwal and Biagioni, 2022). The clinical rating scale for tremor (CRST) is a scoring system used to determine the severity of ET (refer to 'Supplemental Information' section of the policy for additional information). There are two surgical interventions for medication-resistant ET: thalamic ventral intermediate (VIM) nucleus deep brain stimulation (DBS) or unilateral thalamotomy. Magnetic resonance-guided focused ultrasound (MRgFUS) is a noninvasive surgical technology with two components: MRI and high-intensity focused ultrasound. MRI provides detailed images of the brain in real time during surgery, allowing for precision in identifying the target area and minimizing risk to surrounding tissue. The MRgFUS thalamotomy procedure uses high-energy ultrasound beams to create a permanent lesion in the (VIM) nucleus of the thalamus. Bilateral thalamotomy for ET is no longer performed due to an unacceptable rate of side effects, particularly impairment of speech articulation. MRgFUS has also been used to treat uterine fibroids (leiomyomata), metastatic bone cancer, breast tumors, liver tumors, and other types of tumors.

Regulatory Status

In July 2016, the FDA granted premarket approval (PMA) of the ExAblate Neuro System for the treatment of ET in adults aged 22 or older whose tremor has failed pharmacological treatment. ExAblate Neuro uses focused ultrasound to induce a unilateral thalamic lesion (thalamotomy) when the ventralis intermedius has been identified and is accessible for ablation by the device. The intent of treatment is to reduce an individual's ET and increase motor function. This PMA outlined required pending studies for the device, including investigational treatment with the

ExAblate Neuro in 75 patients to be evaluated at 2-, 3-, 4- and 5-years post-operative. The best available published evidence to date on ExAblate Neuro for transcranial thalamotomy in patients with medically refractory ET includes the pivotal randomized, sham-controlled trial (Elias et al., 2016) and the feasibility trial (Elias et al., 2013).

FDA approval was based on the short-term results of a prospective, double-blind, randomized sham-controlled trial in which 76 patients with medically refractory ET were randomly assigned in a 3:1 ratio to focused ultrasound thalamotomy (producing unilateral thermal ablation of the thalamic VIM nucleus) or a sham procedure (Elias et al., 2016). At three months, the thalamotomy group had significantly greater improvement in hand tremor scores than the sham treatment group; the between-group difference in mean change from baseline was 8.3 points and was maintained at 12 months (7.2 points). The thalamotomy group also showed significant improvements in disability and QOL scores. Adverse events were more common in the thalamotomy group at three months, with 36% experiencing gait disturbance and 38% experiencing numbness or paresthesia; these symptoms persisted at 12 months in 9 and 14%, respectively (Elias et al. 2016).

Informational, not addressed in this policy: The FDA approved the use of the ExAblate Model 4000 (Neuro) for the treatment of tremor-dominant Parkinson's disease with medication-refractory tremor through the PMA process On December 16, 2018. Patients must be at least age 30.

COVERAGE POLICY

MRgFUS unilateral thalamotomy may be considered medically necessary as a treatment of ET when **ALL** of the following clinical criteria are met with documentation:

1. Definitive diagnosis of essential tremor; **AND**

2. Moderate to severe tremor of the hand as documented by quantifiable testing such as Clinical Rating Scale for Tremor (defined by a score of ≥ 2 on the CRST) or another nationally accepted clinical measure of tremor severity;

AND

3. Failure of at least **TWO** tremor suppressant medications, including at least one first-line agent (e.g., propranolol or primidone). Failure defined by persistent moderate to severe tremors despite adequate duration and dosing of compliant therapy according to current FDA approved labeling/compendia, intolerable side effects of drug therapy or contraindications. For patients receiving concurrent medical therapy, medication doses should be stable for 30 days. Documentation and supporting rationale required; **AND**

4. Member is 22 years of age or older; **AND**

5. Member is not a candidate for DBS (e.g., due to advanced age, anticoagulant therapy, or surgical complications), or DBS has failed, but there are no retained cranial implants); **AND**

6. MRgFUS unilateral thalamotomy is determined to be the best treatment option for member's specific condition and history according to an evaluation by a multidisciplinary team.

LIMITATIONS AND EXCLUSIONS

The following are considered **contraindications/exclusions** based on insufficient evidence:

1. Bilateral MRgFUS thalamotomy
2. Contralateral to a previous thalamotomy
3. Individual unable to undergo MRI (e.g., non-MRI-compatible implanted metallic devices, or sensitivity to MRI contrast agents; obstructions in the treatment beam path, such as a scar, skin fold, or irregularity, bowel, pubic bone, intrauterine device, surgical slips, or any hard implants; and fibroids that are close to sensitive organs such as the bowel or bladder or are outside the image area)
4. Skull density ratio (ratio of cortical to cancellous bone) is <0.40
5. Additional contraindications to the FDA approved system for the treatment of ET (e.g., ExAblate Neuro System):
   a. Women who are pregnant
   b. Advanced kidney disease or on dialysis
   c. Unstable cardiac status or severe hypertension

d. Behavior(s) consistent with ethanol or substance abuse
e. History of abnormal bleeding, hemorrhage, and/or coagulopathy
f. Currently on anticoagulant or drugs known to increase risk or hemorrhage within one month of focused ultrasound procedure
g. Cerebrovascular disease
h. Brain tumors
i. Unable or unwilling to tolerate the required prolonged stationary position during treatment (approximately two hours)

The following are considered **experimental, investigational, and unproven** based on insufficient evidence:
1. Any indications other than those listed above

SUMMARY OF MEDICAL EVIDENCE

Evidence for the use of MRgFUS in the treatment of medication-refractory ET consists of a double-blind, sham-controlled randomized trial meta-analyses, and technology assessments. One meta-analysis reported significant improvements in hand tremor scores from baseline up to 24 months post-treatment (Miller et al. 2022), with evidence of a diminishing treatment benefit over time. Another meta-analysis found similar improvements in tremor severity with MRgFUS to unilateral DBS, but improvements in both were inferior to bilateral DBS (Giordano et al., 2020). The sham-controlled randomized trial (Elias et al., 2016) which was considered high-quality found significant improvements in the treatment group in tremor severity, functional improvement, and quality of life after 3 months of follow-up, and these results were maintained through 2 years of follow-up.

Agrawal et al. (2021) published a systematic review of 29 studies (N = 617) to analyze the efficacy and the safety profile of MRgFUS for ET. Studies that reported outcomes in patients with tremors secondary to any other causes, such as drug-induced tremor, trauma, psychogenic tremor, or co-morbid Parkinson disease and dystonia were excluded. Of the 29 studies, only one (Elias et al., 2016) was an RCT, the remaining were observational studies. Pre- and post- procedure changes in the CRST score, hand score, disability and QOL scores were evaluated. A significant difference was observed in the pooled standard mean difference between pre- and post-operative total CRST score, hand score, and disability at 12 months. Ataxia was the most common postoperative complication. All complications showed a decreasing trend over time. More than one third of patients developed sonication related complications, amongst which head pain and dizziness were the most common. No hemorrhage, seizure or trajectory related complications were reported. The authors noted that the limitation of this study is noted observational studies formed the majority basis for the analysis as there is only one clinical trial on the subject. The systematic review concluded that currently the MRgFUS procedure appears to be the procedure of choice for patients unable to tolerate an invasive procedure; however, for it to replace established surgical options like DBS, further research will be required to prove long-term clinical efficacy in both unilateral and bilateral procedures.

Several follow-up studies have been conducted to assess the durability of MRI-guided focused ultrasound thalamotomy 2 to 3 years after treatment. Chang et al. (2018) published the 2-year follow-up results of the RCT conducted by Elias et al. (2016). At 6 months after the procedure, the mean hand tremor score improved by 55%. The mean hand tremor motor score had improved by 56% over baseline at 2 years (change in score from baseline to 2 years, 11 points). Halpern et al. (2019) evaluated the outcomes of this same group three years after the procedure. The median hand tremor motor score remained stable, improving by 56% from baseline. Meng et al. (2018) conducted a retrospective review of the 2-year outcomes of 37 patients who underwent unilateral MRgFUS thalamotomy to treat moderate to severe medically refractory ET. At 2 years, the baseline dominant tremor score improved by 42.4%. At one year, 45.7% of individuals had significant tremor improvement; at two years, this had decreased to 35.3%. These follow-up studies show significant drop-out rates, introducing the possibility of retention bias into the results. Additional trials (Halpern, 2019; Park, 2019; Sinai, 2019) with follow-up between 3 and 5 years after the procedure demonstrate a sustained improvement compared to the baseline.

Cosgrove et al. (2022) reported the four- and five-year outcomes of the open-label extension study by Elias et al. (2016). The study evaluated the efficacy, durability, and safety of transcranial MRgFUS thalamotomy for patients with medication refractory ET. Of the 75 treated patients, 45 were observed at four years and 40 at five years. The CRST

was used to determine outcomes, which included hand combined tremor-motor (scale of 0 to 32), functional impairment (scale of 0 to 32), postural tremor (scale of 0 to 4), and total Quality of Life in Essential Tremor Questionnaire (QUEST) scores (scale of 0 to 100). At 48- and 60-months post-treatment, CRST scores for postural tremor remained significantly improved from baseline by 73.3% and 73.1%, respectively. At each time point, combined hand tremor/motor scores improved by 49.5% and 40.4%, respectively. At five years, there were no significant adverse events. At the four- and five-year follow-ups, the study investigators categorized all adverse events as either mild (71%) or moderate (29%). There were no additional AEs due to or possibly connected to the surgery between the 12-month time point and the 5-year follow-up. The loss of patient follow-up at four and five years was cited as a limitation by the author. However, only one of the seven patients who dropped out of the trial after the fourth year had an alternate treatment (DBS); the others dropped out due to concomitant, unrelated health issues and an inability to travel because of the coronavirus disease outbreak in 2019. The authors concluded that five years after unilateral MRgFUS thalamotomy, there was sustained and considerable tremor improvement, an increase in quality of life, and no progressive or delayed adverse effects.

Systematic Reviews / Meta-Analysis

Miller et al. (2022) published a meta-analysis that assessed the efficacy of MRgFUS for treating medication-refractory ET with a focus on long-term trends and response durability. The meta-analysis included 17 prospective studies, three retrospective studies, and one randomized controlled trial. Tremor was assessed using pooled reported effects of hand tremor scores, CRST scores, or the QUEST. The results indicated a continued treatment advantage, but a diminishing treatment effect between 3 and 12 months and 24 months after treatment. The authors stated that this declining effect could be attributable to heterogeneity within the studies, disease progression, or a true waning effect with time. DBS has also been associated with diminished effects, which can be attributed to disease progression or habituation. There authors noted that are no studies that directly compare MRgFUS and DBS.

Giordano et al (2020) performed a meta-analysis to compare unilateral MRgFUS versus unilateral and bilateral DBS for medication-refractory ET. There were 45 studies found between 1996 and 2019. DBS was analyzed in 37 trials (n=1202), while MRgFUS was evaluated in 8 studies (n=477); 15 studies were designed retrospectively, whereas 30 were designed prospectively and 30 trials were designed prospectively, whereas 15 were designed retrospectively. The average percentage improvement in tremor severity was substantially higher in the pooled DBS group (60.1%±9.7%) than in the MRgFUS group (55.6%±8.2%). Subgroup analysis indicated that bilateral DBS (61.2%±5.2%) improved tremor severity significantly more than unilateral DBS (56.4%±9.7%) and MRgFUS, with no significant difference between unilateral DBS and MRgFUS. MRgFUS was associated with considerably better measures of average percentage increase in QOL than DBS (61.9%±7.9% vs 52.5%±16.2%). There were 517 complications reported in the DBS group and 484 complications reported in the MRgFUS group. The most common adverse events associated with DBS were lead-related problems (11.4%) and speech difficulties (11.1%). The most common adverse effects associated with MRgFUS were sensory (36.7%) and gait disturbances/muscle difficulties (34.4%). Limitations of the analysis included the various scales used in studies to quantify tremor severity and QOL. Only one retrospective study compared DBS and MRgFUS.

Mohammed et al. (2018) conducted a systematic review and meta-analysis to analyze the overall outcomes and complications of MRgFUS in the treatment of ET. Patients with the diagnosis of ET who were treated with MRgFUS were included in the study. The change in the CRST score after treatment was analyzed. Nine studies with 160 patients who had ET were included in the meta-analysis. Dizziness was the most common in-procedure complication, occurring in 45.5%, followed by nausea and vomiting in 26.85%. Pooled analyses found significant improvements in the mean percentage change in CRST scores (62.2%) and QOL in ET scores (46.5%). Complications included nausea, vomiting, and ataxia, which decreased during the 12-month follow-up. However, a high probability of bias due to study design, limited follow-up, small sample size, and a lack of comparative evidence evaluating MRgFUS and DBS was noted.

Technology Assessments

Health Quality Ontario (2018) published a technology assessment that included nine studies: four single cohort studies, two retrospective chart reviews, two uncontrolled prospective studies, and one RCT (Elias et al. 2016). The sham treatment was compared in the RCT, while DBS and radiofrequency thalamotomy were compared in the chart reviews. The GRADE system was used to assess study quality. The RCT received a high-quality rating, while the uncontrolled comparative studies received a very low-quality rating, and the remaining studies received a low-quality rating. Tremor

severity was reported as an outcome in all studies. Because of differences in study designs, analyses, and outcomes, no results were pooled. Overall, the reviewers concluded that MRgFUS reduced tremor severity and improved QOL.

Hayes published a Technology Assessment (HTA) in 2019 (reviewed in 2021 and archived in May 2022) that assessed the use of unilateral MRgFUS thalamotomy for the treatment of moderate-to-severe treatment-resistant ET. The authors identified 5 eligible studies with patients who had moderate to severe medication-refractory ET. These studies compared MRgFUS to DBS, radiofrequency thalamotomy and sham treatment with follow-up ranging from 3 months to 4 years: DBS was compared in 2 studies (Huss et al., 2015; Kim et al., 2017), radiofrequency thalamotomy in 1 study (Kim et al., 2017), and sham treatment in 1 study (Elias et al., 2016). Follow-up periods ranged from 3 months to 4 years. Results suggest that unilateral MRgFUS thalamotomy may result in a statistically significant improvement in contralateral hand tremor; however, the clinical significance of this improvement has not been established. Additionally, MRgFUS did not result in improvements in axial tremors of the head, trunk, voice, or ipsilateral tremors. Substantial uncertainty arises from the individual study quality, inconsistency in the evidence, and lack of comparative evidence. The review concluded that a very-low-quality body of evidence is insufficient to draw conclusions regarding benefit (of the 5 eligible studies, 1 was fair quality, 1 was poor quality, and 3 were very poor quality). This quality rating is primarily due to the individual study quality, inconsistency in the evidence, and lack of comparative evidence.

National and Specialty Organizations

The **American Society for Stereotactic and Functional Neurosurgery (ASSFN)** issued a position statement on MRgFUS for the Treatment of ET and recommends MRgFUS as a therapy option for patients with ET when specific criteria are met. The ASSFN statement also notes that there is insufficient evidence to support treatment of tremors of the head, voice or neck with MRgFUS. Furthermore, the guideline noted the absence of direct comparative research of surgical treatment techniques and the improbability that such studies will be conducted due to differences in indications, patient choice, and follow-up needs.

The **American Academy of Neurology (AAN) Quality Standards Subcommittee** published the *Evidence-Based Guideline Update: Treatment of Essential Tremor* which was reaffirmed in 2022. The guideline includes recommendations for pharmacological and nonpharmacological agents. Regarding the decision to use thalamotomy or DBS, the guideline states that it is contingent on the patient's circumstances and risk for intraoperative complications compared to feasibility of stimulator monitoring and adjustments. It is noted that DBS has fewer adverse events when compared to thalamotomy. (Zesiewicz et al., 2022 & 2017).

The AAN also published the *Essential Tremor: Quality Measurement Set* (Zesiewicz et al., 2017) – it contains the following measurement categories:

- Pharmacological Treatment for Patients with ET
- Surgical Evaluation for Patients with ET
- Annual Assessment of Essential Tremor Severity
- Annual Screening of Depression and Anxiety for Patients with ET
- Annual Assessment of Quality of Life for Patients with ET
- Promotion of ET Resources

The **International Parkinson and Movement Disorder Society (IPMDS)** published an evidence-based review of ET treatments (Ferreira 2019). According to the task force, unilateral MRgFUS thalamotomy is "likely efficacious." According to the task force, unilateral MRgFUS thalamotomy is "possibly useful" in clinical practice. The society's recommendation is based on the RCT conducted by Elias (2016).

The **National Institute for Health and Care Excellence (NICE)** issued guidance on unilateral MRgFUS thalamotomy in treatment-resistant ET; no major safety concerns were identified but current evidence of efficacy was limited in quantity. The guideline recommends that this procedure should not be used unless there are special arrangements for clinical governance, consent, and audit or research. NICE suggests that future research include the identification of patient selection criteria and long-term follow-up data (NICE, 2018).

SUPPLEMENTAL INFORMATION

Tremor Scoring System

- The **clinical rating scale for tremor (CRST)** is a scoring system for determining the severity of ET. The CRST is divided into three sections. Part A assesses the tremor, Part B assesses task performance, and Part C assesses the disability caused by the tremor. The three parts add up to a total of 160 points; higher scores indicate a more severe tremor. Part A is the primary clinical end point of interest, with a score range of 0 to 32 summarizing 8 items. The CRST scores at baseline and posttreatment were recorded. A score of two or more on the CRST's postural or action item (ranging from 0-4) and significant disability in at least two daily activities from the disability subsection indicate moderate to severe tremor. (Mohammed et al. 2018)
- The Quality of Life in Essential Tremor Questionnaire (QUEST) scoring was also used to evaluate the QOL improvement following the treatment. The QUEST is scored from 0% to 100%; higher scores reflect a greater perceived disability.

CODING & BILLING INFORMATION

CPT Code

CPT	Description
0398T	Magnetic resonance image guided high intensity focused ultrasound (MRgFUS), stereotactic ablation lesion, intracranial for movement disorder including stereotactic navigation and frame placement when performed

HCPCS Codes – N/A

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

2/8/2023	Policy revised. Updated coverage position to medically necessary and added coverage criteria to 'Coverage Policy' section, and Updated 'Overview' and 'Summary of Evidence' section. Updated references.
2/9/2022	Policy reviewed and updated. No changes in coverage position. Updated references.
2/8/2021	Policy reviewed, no changes to criteria; included guidelines from the American Society for Stereotactic and Functional Neurosurgeons (ASSFN) & Health Quality Ontario (HQO).
4/23/2020	Policy reviewed, no changes.
9/18/2019	Policy reviewed, no changes.
7/10/2018	New policy. IRO Peer Review 4/23/2018. Reviewed by practicing physician board-certified in Neurology.

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Peer Reviewed Publications

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Other Reference (considered in the development of policy; not cited)

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