MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
19 02 2020

Agenda Item No	
National Programme	Trauma
Clinical Reference Group	Neurosciences
URN	1904

Title
Transcranial magnetic resonance guided focused ultrasound thalamotomy for treatment of medication-refractory essential tremor (adults)

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its approval as an IYSD

Proposition
Routinely commission Magnetic resonance guided focused ultrasound thalamotomy for medication refractory patients with essential tremor who fulfil the criteria within the draft policy.

Clinical Panel recommendation
Select appropriate option: The Clinical Panel recommended that the policy progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report
2.	The Head of Acute Programmes / Head of Mental Health Programme confirms the proposal is supported by an: Impact Assessment; Stakeholder Engagement Report; Consultation Report; Equality Impact and Assessment Report; Clinical Policy Proposition. The relevant National Programme of Care Board has approved these reports.

3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Consultation Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality Impact and Assessment Report

No	*Outcome measures*	*Summary from evidence review*
1.	Survival	Not reported
2.	Progression free survival	Not reported
3.	Mobility	Not reported
4.	Self-care	Not reported
5.	Usual activities	Not reported
6.	Pain	Not reported
7.	Anxiety / Depression	Not reported
8.	Replacement of more toxic treatment	Not reported
9.	Dependency on care giver / supporting independence	Not reported
10.	Safety	Adverse effects are unwanted or harmful results of treatment. Kim et al 2017 report the following adverse effects: • TcMRgFUS thalamotomy: mild facial paresis for first month after procedure: 1/23 (4%); balance problems due to brain oedema for first month after procedure, controlled with oral steroid therapy plus mild facial paresis still present at 12 month 1/23 (4%). • Deep brain stimulation (DBS): mild facial paresis for first month after procedure: 1/19 (5%); balance problems relieved with

		stimulation adjustment 3/19 (16%); muscle twitching in the contralateral forearm 1/19 (5%). Avoiding adverse effects is of high value to patients. Kim et al 2017 has a number of serious methodological weaknesses. Treatment allocation was not apparently concealed, so both participants and assessors may have been aware of which treatment was used, introducing potential bias. The method by which treatments were allocated was not reported, so patients with different prognoses may have been preferentially allocated to one or other treatment. The study was retrospective, and the authors do not report whether all eligible patients were included, introducing the possibility of further bias. Also, the authors do not report how many people were treated but not included because they were lost to follow-up; such patients may have had worse outcomes, introducing a further bias. The results are therefore of limited value.
11.	Delivery of intervention	Not reported

No	Outcome measure	Summary from evidence review
1.	Incremental cost effectiveness ratio	An incremental cost effectiveness ratio (ICER) is the ratio of the extra costs of an intervention, above that of alternatives, to the extra benefits it provides. Li et al 2019 report DBS vs TcMRgFUS thalamotomy to have an incremental cost of C$34,026 (£20,200), incremental utility of 0.26 quality-adjusted life years (QALYs) over 5 years and an incremental cost utility C$130,850 (£77,700) per QALY. A lower incremental cost effectiveness ratio indicates better value for money. This does not directly benefit individual patients but means that more patients can be treated with the resources available. This study appears to suggest that DBS is not a cost effective alternative to TcMRgFUS thalamotomy. However, this conclusion rests on potentially unsound foundations. Li et al's cost inputs were for Canada, and obtained from Ontario sources, published literature, clinical expert opinion and the manufacturer of MRgFUS device. The authors' utility estimates were derived from Herceg et al (2012), a study of drug treatment of essential tremor. Since this study was uncontrolled, the placebo effect may have exaggerated apparent treatment effects and therefore the utility gain from treatment. The ICER of DBS versus TcMRgFUS thalamotomy was sensitive to several assumptions related to DBS, including battery life, onset of benefit, risk of hardware complications, and risk of infection. However, none of the sensitivity analyses brought the cost within the usual affordability range. The authors do not report how capital costs of TcMRgFUS thalamotomy equipment was handled in this modelling; if it was excluded from the model, then adding it would

		decrease the incremental cost of DBS and improve its ICER. Canadian healthcare costs differ from those in the NHS, reducing the relevance of this analysis to the NHS.
2.	Successful treatment at one month	The authors defined successful treatment as absent tremor (complete remission) or occasional tremor (greater than 90% improvement) on the Fahn-Tolosa-Marin scale[1]. Kim et al 2017 report rates of successful treatment at one month of 21/23 (91%) after TcMRgFUS thalamotomy and 17/19 (89%) after DBS (no p-value reported). Successful treatment would be of high value to patients. See above for the limitations of Kim et al 2017.
3.	Complete remission at one month	The authors defined complete remission as absent tremor. Kim et al 2017 report rates of complete remission at one month of 10/23 (43%) after TcMRgFUS thalamotomy and 6/19 (32%) after DBS (no p-value reported). Complete remission would be of very high value to patients. See above for the limitations of Kim et al 2017.
4.	Successful treatment at twelve months	The authors defined successful treatment as absent tremor (complete remission) or occasional tremor (greater than 90% improvement) on the Fahn-Tolosa-Marin scale[2]. Kim et al 2017 report rates of successful treatment at twelve months of 18/23 (78%) after TcMRgFUS thalamotomy and 16/19 (84%) after DBS, (no p-value reported). Successful treatment would be of high value to patients. See above for the limitations of Kim et al 2017.
5.	Complete remission at twelve months	The authors defined complete remission as absent tremor. Kim et al 2017 report rates of complete remission at twelve months of 8/23 (35%) after TcMRgFUS thalamotomy and 9/19 (32%) after DBS (no p-value reported). Complete remission would be of very high value to patients. See above for the limitations of Kim et al 2017.
6.	Change in CRST total score	The Clinical Rating Scale for Tremor (CRST) scale is used to assess the severity of tremor. It has three parts: Part A (observed tremor), Part B (tasks) and Part C (disability), each scored from 0 to

[1] This scale contains sections for assessing rest, postural and kinetic/ intention tremor amplitude in specific anatomic locations (part A), tremor in writing, drawing, and pouring (part B), activities of daily living (part C), and global assessments by the patient and examiner (part D), with each item rated on a scale from 0 to 4. Higher scores indicate worse tremor.

[2] This scale contains sections for assessing rest, postural and kinetic/ intention tremor amplitude in specific anatomic locations (part A); tremor in writing, drawing, and pouring (part B); activities of daily living (part C); and global assessments by the patient and examiner, with each item rated on a scale from 0 to 4. Higher scores indicate worse tremor.

		4; higher scores indicate more severe tremor. Part A separately scores resting, postural, and action or intention components of hand tremor. Huss et al 2015 report the following post-procedure scores (percentage improvement from baseline): • bilateral DBS 13.2 (79.5%) • unilateral DBS 15.8 (62.8%) • TcMRgFUS thalamotomy 17.7 (55.7%). All three procedures are reported as improved versus baseline ($p<0.05$), and the second two procedures are reported as different from bilateral DBS ($p<0.05$). Improvement in tremor would be of high value to patients. However, this study has numerous serious methodological weaknesses. Treatment allocation was not apparently concealed, so both participants and assessors may have been aware of which treatment was used, introducing potential bias. The study was retrospective, and the authors do not report whether all eligible patients were included, introducing the possibility of further bias. Allocation to unilateral or bilateral DBS treatment depended on whether the participant had unilateral or bilateral tremor, though three participants with bilateral symptoms "chose not to have the second side treated after unilateral [DBS] placement", three "were recommended for unilateral treatment because of concerns regarding potential complications because of age and less cognitive reserve" and three others "had physical considerations (brain, skull, or scalp) that precluded bilateral treatment". The comparison is therefore potentially biased by the inclusion in the TcMRgFUS thalamotomy group of patients with less extensive disease. This is corroborated by CRST scores indicating more severe disease in participants allocated to DBS. Similarly, the authors carried out 18 tests of statistical significance on their reported results of treatment, did not adjust the p-value and regarded as statistically significant those where $p<0.05$. Since they do not report p-values, we cannot tell which if any of these differences was significant with the correct, adjusted p-value of 0.00278. Twelve patients, all treated with DBS, had "missing information or incomplete evaluations" and were excluded from the analysis. These patients may have had worse outcomes, introducing further bias. Since one participant with only three months of follow-up was included, it is unclear what the exclusion criteria were. Participants undergoing unilateral DBS had shorter follow-up, though the authors report no test of the significance of this difference. For patients who underwent DBS, postoperative evaluation took place 3 to 24 months (mean follow-up, 13 months) after the patient's device was turned on. For patients who underwent TcMRgFUS thalamotomy, CRST was evaluated at 12 months after surgery, except for one patient who only had a 3-month follow-up. These differences in follow-up are further source of bias. Although higher QUEST scores indicate worse quality of life (confirmed by the authors ("QUEST summary index, (100% is worst)"), participants are reported as having higher QUEST scores after the procedures than before. Yet the authors

		report “After surgery, patients in both groups reported significant improvements in overall quality of life”. This contradiction casts further doubt on the reliability of the paper. We raised this issue with the authors, but have received no reply. For unilateral DBS procedures, “too few patients had preoperative and postoperative QUEST scores, so these patients were excluded from analysis of QUEST outcomes”. Bilateral DBS results are of limited relevance to this RER, as TcMRgFUS thalamotomy was only used for patients with unilateral tremor.
7.	QUEST summary score	The Quality of Life in Essential Tremor Questionnaire (QUEST) includes 30 items in five domains (physical, psychosocial, communication, leisure and work/finance). Higher scores indicate lower quality of life. Huss et al 2015 report the following mean pre- and post-procedure scores: • bilateral DBS 52.1, 72.0 • unilateral DBS not reported • TcMRgFUS thalamotomy 37.5, 17.7. Both post-procedure scores reported as improved versus baseline ($p<0.05$), but not showing different improvement between procedures. Improvement in quality of life would be of very high value to patients. See above for the limitations of Huss et al 2015.
8.	Proportion of participants with CRST handwriting score of 2 to 4 in dominant hand pre-procedure who had a tremor score of 0 to 1 post-procedure	This outcome covers the proportion of participants reporting a degree of improvement in handwriting. Huss et al 2015 report the following post-procedure scores (percentage improvement from baseline): • bilateral DBS 46/55 (83.6%) • unilateral DBS 11/13 (84.6%) • TcMRgFUS thalamotomy 12/15 (80%). The differences between these proportions are reported as not statistically significant. Improvement in handwriting would be of value to patients. See above for the limitations of Huss et al 2015.
9.	Proportion of participants with CRST handwriting score of 3 or 4 (illegible) pre-procedure who had a tremor score	This outcome covers the proportion of participants reporting a degree of improvement in handwriting. Huss et al 2015 report the following post-procedure scores (percentage improvement from baseline): • bilateral DBS 20/26 (76.9%) • unilateral DBS 7/8 (87.5%) • TcMRgFUS thalamotomy 6/7 (86.7%) The differences between these proportions are reported as not statistically significant.

	of 0 to 2 post-procedure	Improvement in handwriting would be of value to patients. See above for the limitations of Huss et al 2015.

TcMRgFUS thalamotomy for essential tremor compared with sham treatment

No	*Outcome measures*	*Summary from evidence review*
1.	Survival	Not reported
2.	Progression free survival	Not reported
3.	Mobility	Not reported
4.	Self-care	Not reported
5.	Usual activities	Not reported
6.	Pain	Not reported
7.	Anxiety / Depression	Not reported
8.	Replacement of more toxic treatment	Not reported
9.	Dependency on care giver / supporting independence	Not reported
10.	Safety	Adverse effects are unwanted or harmful results of treatment. Elias et al 2016 report the following adverse effects of TcMRgFUS thalamotomy: gait disturbance (36%), paraesthesias or numbness (38%), persisting for 12 months in 9% and 14% of patients, respectively. One patient had dense and permanent hypaesthesia of the dominant thumb and index finger, categorised as a serious adverse event. One patient had a transient ischaemic attack 6 weeks after undergoing thalamotomy. Avoiding adverse effects is of high value to patients. This is a reliable randomised trial, which included independent analysis of videotapes by neurologists. Despite blinding, 95% of patients who underwent active treatment and 80% of those who underwent the sham procedure correctly guessed their assignment immediately after the procedure. However, the improvements are unlikely to be the result of chance or bias.
11.	Delivery of intervention	Not reported

No	Outcome measure	Summary from evidence review
1.	Change in mean CRST hand tremor score[3] at 3 months	This hand tremor score (on a scale ranging from 0 to 32, with higher scores indicating more severe tremor) was derived from the CRST, Part A (three items: resting, postural, and action or intention components of hand tremor), and the CRST, Part B (five tasks involving handwriting, drawing, and pouring), in the hand contralateral to the thalamotomy. Elias et al 2016 report the following results: • TcMRgFUS thalamotomy: pre-treatment 18.1, post-treatment 9.6 • sham: pre-treatment 16.0, post-treatment 15.8 • difference: 8.3 points, 95% confidence interval (CI) 5.9 to 10.7, p<0.001. Improvement in hand tremor would be of high value to patients. See above for the limitations for Elias et al 2016.
2.	Change in mean CRST hand tremor score at 12 months	This hand tremor score (on a scale ranging from 0 to 32, with higher scores indicating more severe tremor) was derived from the CRST, Part A (three items: resting, postural, and action or intention components of hand tremor), and the CRST, Part B (five tasks involving handwriting, drawing, and pouring), in the hand contralateral to the thalamotomy. Elias et al 2016 report the following results: • TcMRgFUS thalamotomy: pre-treatment 18.1, post-treatment 10.9 • sham not reported • difference between treatments 7.2 points, 95% CI 6.1 to 8.3, p<0.001. Improvement in hand tremor would be of high value to patients. See above for the limitations for Elias et al 2016.
3.	Change in mean CRST disability score at 3 months	The CRST disability score is derived from Part C of CRST, which measures functional disability. Elias et al 2016 report the following results: • TcMRgFUS thalamotomy: pre-treatment 16.5, post-treatment 6.2 • sham: pre-treatment 16.0, post-treatment 15.6 • difference: 9.9 points, p<0.001. Improvement in disability would be of high value to patients.

[3] The tremor score (on a scale ranging from 0 to 32, with higher scores indicating more severe tremor) was derived from the CRST, Part A (three items: resting, postural, and action or intention components of hand tremor), and the CRST, Part B (five tasks involving handwriting, drawing, and pouring), in the hand contralateral to the thalamotomy.

		See above for the limitations for Elias et al 2016.
4.	Change in mean QUEST score at 3 months	The Quality of Life in Essential Tremor Questionnaire (QUEST) includes 30 items in five domains (physical, psychosocial, communication, leisure and work/finance). Higher scores indicate lower quality of life. Elias et al 2016 report the following results: • TcMRgFUS thalamotomy: pre-treatment 42.6, post-treatment 23.1 • sham: pre-treatment 42.8, post-treatment 41.1 • difference: 17.8 points, p<0.001. Improvement in quality of life would be of very high value to patients. See above for the limitations for Elias et al 2016.

TcMRgFUS thalamotomy for essential tremor compared with no treatment

No	*Outcome measures*	*Summary from evidence review*
1.	Survival	Not reported
2.	Progression free survival	Not reported
3.	Mobility	Not reported
4.	Self-care	Not reported
5.	Usual activities	Not reported
6.	Pain	Not reported
7.	Anxiety / Depression	Not reported
8.	Replacement of more toxic treatment	Not reported
9.	Dependency on care giver / supporting independence	Not reported
10.	Safety	Not reported
11.	Delivery of intervention	Not reported

No	Outcome measure	Summary from evidence review
1.	Incremental cost effectiveness ratio	An incremental cost effectiveness ratio (ICER) is the ratio of the extra costs of an intervention, above that of alternatives, to the extra benefits it provides. Li et al 2019 report TcMRgFUS thalamotomy vs no treatment to have an incremental cost of C$21,438 (£12,700), incremental utility of 0.47 QALYs over 5 years and an incremental cost utility $45,817 (£27,200) per QALY, within normal NHS value for money limits. A lower incremental cost effectiveness ratio indicates better value for money. This does not directly benefit individual patients, but means that more patients can be treated with the resources available. This study appears to suggest that TcMRgFUS thalamotomy is a cost effective alternative to no treatment. This study appears to suggest that TcMRgFUS thalamotomy is a cost effective alternative to no treatment. However, this conclusion rests on potentially unsound foundations. Li et al's cost inputs were for Canada, and obtained from Ontario sources, published literature, clinical expert opinion and the manufacturer of MRgFUS device. The authors' utility estimates were derived from Herceg et al (2012), a study of drug treatment of essential tremor. Since this study was uncontrolled, the placebo effect may have exaggerated apparent treatment effects and therefore the utility gain from treatment. The authors' sensitivity analysis indicated that the incremental cost-effectiveness (ICER) of TcMRgFUS thalamotomy versus no surgery was most sensitive to assumptions regarding baseline utility, underlining the importance of this issue. In their base-case comparison of TcMRgFUS thalamotomy and no surgery, the authors disregarded the capital cost of TcMRgFUS thalamotomy equipment. Including it, a more realistic approach which reflects cost to the healthcare system, almost doubled the ICER to C$85,047 (£50,500) per QALY), beyond what is considered value for NHS money. Canadian healthcare costs differ from those in the NHS, reducing the relevance of this analysis to the NHS in England.

TcMRgFUS thalamotomy for essential tremor (no comparator)

No	*Outcome measures*	*Summary from evidence review*
1.	Survival	Not reported
2.	Progression free survival	Not reported
3.	Mobility	Not reported
4.	Self-care	Not reported

5.	Usual activities	Not reported
6.	Pain	Not reported
7.	Anxiety / Depression	Not reported
8.	Replacement of more toxic treatment	Not reported
9.	Dependency on care giver / supporting independence	Not reported
10.	Safety	Adverse effects are unwanted or harmful results of treatment. Chang et al 2018 report that none of the adverse events reported in Elias et al 2016 worsened at 2 years follow-up, and 2 of these events resolved (dysergia and paraesthesia). There were no new adverse events in the participants reported during the second year of follow-up. Avoiding adverse effects is of high value to patients. There are concerns about the reliability of this study. The authors report that “many” of the participants who were not followed-up “had unsuccessful treatment or suboptimal benefit”. The exclusion of non-responders from the analysis introduces a bias and an overestimate of the benefit in those patients that remained in the study.” Elias et al 2016 reported mean pre-treatment hand tremor scores derived from CRST Parts A and B of 18.1 in the TcMRgFUS thalamotomy group and 16 in the sham group. Chang et al 2018 reports a mean pre-treatment hand tremor score derived in the same way from all 76 participants of 19.8, higher than in either of the constituent groups. Furthermore, the authors’ reported 95% CIs for changes in CRST scores do not include the reported value for this parameter. These discrepancies cast doubt on the accuracy of the data reported in this study.
11.	Delivery of intervention	Not reported

No	Outcome measure	Summary from evidence review
1.	Change in mean CRST hand tremor score at 24 months	This hand tremor score (on a scale ranging from 0 to 32, with higher scores indicating more severe tremor) was derived from the CRST, Part A (three items: resting, postural, and action or intention components of hand tremor), and the CRST, Part B (five tasks involving handwriting, drawing, and pouring), in the hand contralateral to the thalamotomy.

		Chang et al 2018 report the following results: • pre-treatment 19.8 • post-treatment 8.8 • difference 11 points, 95% CI 7.6 to 10.0 points, p<0.001. Improvement in hand tremor would be of high value to patients. See above for the limitations of Chang et al 2018.
2.	Change in mean CRST disability score at 24 months	This disability score was derived from the CRST Part C. Chang et al 2018 report the following results: • pre-treatment 16.4 • post-treatment 6.5 • difference 9.9 points, 95% CI 5.3 to 7.7 points, p<0.001. Improvement in disability would be of high value to patients. See above for the limitations of Chang et al 2018.

Considerations from review by Rare Disease Advisory Group
Not applicable / [TO BE COMPLETED BY AC WHERE APPLICABLE]

Pharmaceutical considerations
TO BE COMPLETED BY NHS ENGLAND

Considerations from review by National Programme of Care
Select appropriate option: 1) The proposal received the full support of the Trauma PoC Assurance Group on the 7th February 2020