CLINICAL PRIORITIES ADVISORY GROUP
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Agenda Item No	3.1
National Programme	Trauma
Clinical Reference Group	Neurosurgery
URN	2006

Title
MR-guided laser interstitial thermal therapy (MRgLITT) for children and adults with refractory focal epilepsy

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend the relative priority

Proposition
For routine commissioning MRgLITT for treatment of epileptogenic zones is recommended to be available as a routine commissioning treatment option for children and adults with refractory focal epilepsy. MRgLITT provides a minimally invasive technique for patients who have epilepsy which is not controlled on medication and that meet the commissioning criteria within the policy. This provides these patients with a surgical option or in those who could have high risk open neurosurgery, it provides an alternative option with less damage to surrounding structures. The aim is to reduce seizure frequency for these patients and improve their safety and quality of life.

Clinical Panel recommendation
The Clinical Panel recommended that the policy proposition 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 Programme confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care 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.	Engagement Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

In adults and children with drug-resistant focal epilepsy who have hypothalamic hamartoma what is the clinical effectiveness and safety of MRgLITT compared with continued medical therapy, and in adults and children with drug-resistant focal epilepsy who have identifiable epileptogenic zones what is the clinical effectiveness and safety of MRgLITT compared with open neurosurgical resection or continued medical therapy alone?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Seizure freedom **Certainty of evidence:** Very low	Seizure freedom is key to patients and their carers because it can result in reduced hospital admissions and outpatient attendance, reduced reliance on medication as well as improved health over time and improved quality of life.
	Children and adults with refractory focal epilepsy caused by hypothalamic hamartoma unsuitable for neurosurgical resection. Three studies (one SRMA of four case series and two retrospective case series) provided evidence relating to seizure freedom for people with hypothalamic hamartoma treated with MRgLITT. Seizure freedom was measured at different time points up to a mean of >17.5 months and was defined using the Engel classification [a] (Wang et al 2020), the

	International League Against Epilepsy (ILAE) [b] classification (Xu et al 2018) or no definition (Curry et al 2018). At more than six months follow-up: • one meta-analysis of four case series (Wang et al 2020) (n=83) reported a mean seizure free (Engel class I) rate of 99% (95% CI 92% to 100%). (**VERY LOW**) At mean 6.3 months (+/- 4.8 months) follow-up: • one case series (Xu et al 2018) (n=15) reported a rate of good gelastic seizure control (ILAE class 1-3) of 73% (no CI reported). (**VERY LOW**) At less than one year's follow-up: • one case series (Curry et al 2018) (n in this outcome not stated, total n=71) reported a rate of freedom from gelastic seizures (not defined) of 78% (no CI reported). (**VERY LOW**) At one year's follow-up • one case series (Curry et al 2018) (n in this outcome not stated, total n=71) reported a rate of freedom from gelastic seizures not defined) of 93% (no CI reported). (**VERY LOW**) At mean >17.5 months (+/- 7.5 months) follow-up: • one case series (Xu et al 2018) (n=15) reported a rate of freedom from gelastic seizures (ILAE class 1) of 80% (no CI reported). (**VERY LOW**) At mean >17.5 months (+/- 7.5 months) follow-up: • one case series (Xu et al 2018) (n=15) reported a rate of well-sustained gelastic seizure control (ILAE class 1-2) of 93% (no CI reported). (**VERY LOW**) At mean >17.5 months (+/- 7.5 months) follow-up: • one case series (Xu et al 2018) (n=9) reported a rate of freedom from non-gelastic seizures (ILAE class 1) of 56% (no CI reported). (**VERY LOW**) At mean >17.5 months (+/- 7.5 months) follow-up: • one case series (Xu et al 2018) (n=9) reported a rate of well-sustained non-gelastic seizure control (ILAE class 1-2) of 67% (no CI reported). (**VERY LOW**) At mean >17.5 months (+/- 7.5 months) follow-up: • one case series (Xu et al 2018) (n=9) reported a rate of ILAE class 4 non-gelastic seizures of 11% (no CI reported). (**VERY LOW**) At mean >17.5 months (+/- 7.5 months) follow-up: • one case series (Xu et al 2018) (n=9) reported a rate of ILAE class 5 non-gelastic seizures of 22% (no CI reported). (**VERY LOW**) **These studies provided very low certainty evidence from non-comparative case series that between 92-100% of patients with drug-resistant focal epilepsy who had hypothalamic hamartoma**

	were not having disabling seizures (Engel class I) more than 6 months after MRgLITT. **Of patients who had suffered from gelastic seizures, at mean 6.3 months follow-up after MRgLITT, 73% were reported to have good seizure control (ILAE class 1-3) and at between less than one year to mean >17.5 months follow-up, between 78% and 93% were reported to be free of gelastic seizures (ILAE class 1 or no definition).** **Of patients who had suffered from non-gelastic seizures, at mean >17.5 months follow-up after MRgLITT, 56% were reported to be free of non-gelastic seizures and 67% were reported to have well-sustained seizure control (ILAE class 1-2). 11% were reported to have ILAE class 4 seizures (between four seizure days a year and a 50% reduction in seizure days) and 22% to have ILAE class 5 seizures (between less than 50% reduction and 100% increase in seizure days).**
	Children and adults with refractory focal epilepsy when open neurosurgery carries a high risk of serious adverse effects. Seven studies (three SRMAs of between nine and sixteen case series, one comparator cohort study and three case series) provided evidence relating to seizure freedom for people with drug-resistant focal epilepsy with identifiable epileptogenic zones treated with MRgLITT. Three studies reported outcomes for patients with epilepsy due to different aetiologies grouped together, six reported outcomes for patients with epilepsy of temporal lobe origin, and two also reported outcomes separately for patients with epilepsy due to other specific aetiologies. Seizure freedom was measured at different time points between 7 days and 51 months after the procedure and was defined using the Engel classification [1] in six studies (Drane et al 2015, Gross et al 2018, Landazuri et al 2020, Sanjeet et al 2019, Wang et al 2020, Xue et al 2018), and as 'free of disabling seizures' with no specific definition in one study (Bermudez et al 2020). *For patients with drug-resistant focal epilepsy due to a mix of aetiologies:* At more than six months follow-up: • One SRMA of 16 case series including adults and children with a range of aetiologies (Wang et al 2020) (n=414) reported a mean seizure free (Engel class I) rate of 65% (95% CI 56 to 74) (I^2=69.42 (p=0.00)). **(VERY LOW)** At 12 months follow-up: • One case series of patients with drug-resistant epilepsy (DRE) with a range of aetiologies (Landazuri et al 2020) (n=42) reported a rate of Engel class I seizures of 64.3% (95% CI 48.0 to 78.5), Engel class II seizures of 9.5% (no CI reported), Engel class III seizures of 21.4% (no CI reported) and Engel class IV seizures of 4.8% (95% CI 0.6 to 16.2). **(VERY LOW)** At 7 days to 51 months follow-up: • Xue et al 2018 carried out meta-analyses of case series of adults and children with DRE with focal onset of seizures who had a

	range of aetiologies. Meta-analysis of 12 case series (n=189) reported a pooled prevalence of Engel class I seizures of 61% (95% CI 54 to 68) (I^2=14.5% (p=0.302)). Meta-analysis of seven case series (n=135) reported a pooled prevalence of Engel class II seizures of 12% (95% CI 7 to 16) (I^2=86.8% (p=0.000)). Meta-analysis of six case series (n=135) reported a pooled prevalence of Engel class III seizures of 18% (95% CI 10 to 22) (I^2=3.0% (p=0.397)). Meta-analysis of five case series (n=109) reported a pooled prevalence of Engel class IV seizures of 15% (95% CI 8 to 22), (I^2=13.2% (p=0.330)). **(VERY LOW)** *For patients with drug-resistant focal epilepsy of temporal lobe origin:* At six months follow-up: • One comparator cohort study including adults with mesial temporal lobe epilepsy (Drane et al 2015) (n=58) reported that of 10 subjects having SLAH on their language dominant hemisphere, 7, 1, 2 and 0 had Engel class I, II, III and IV seizures respectively; of 22 subjects having open resection on their language dominant hemisphere 11, 5, 3 and 3 had Engel class I, II, III and IV seizures respectively; of 9 subjects having SLAH on their non-dominant hemisphere 4, 0, 2 and 3 had Engel class I, II, III and IV seizures respectively; and of 17 subjects having open resection on their non-dominant hemisphere 13, 2, 2 and 0 had Engel class I, II, III and IV seizures respectively (no significance measures reported). The authors did not calculate seizure freedom rates; based on the numbers reported, for subjects having intervention on their dominant hemisphere a higher proportion were seizure free after SLAH than open resection, and for subjects having intervention on their non-dominant hemisphere a higher proportion were seizure free after open resection than SLAH. However numbers were small and no significance measures were reported for seizure outcomes so it is not possible to draw conclusions about seizure freedom in relation to the MCID [1]. **(VERY LOW)** At more than six months follow-up: • One SRMA of 12 case series including adults and children with temporal lobe epilepsy (n=266), (Wang et al 2020) reported a mean seizure free rate of 59% (95% CI 53 to 65), (I^2 =0.00, (p=0.83)). **(VERY LOW)** At mean 8.3 (+/- 1.27) months follow-up: • One case series reported a rate of freedom from disabling seizures (not defined) of 85% (no CI reported) in patients with focal epilepsy of mesial temporal origin who had had MRgLITT on their dominant hemisphere (Bermudez et al 2020) (n=13). **(VERY LOW)** At mean 8.5 (+/- 4.6) months follow-up: • One case series reported a rate of freedom from disabling seizures (not defined) of 75% (no CI reported) in patients with focal epilepsy of mesial temporal origin who had had MRgLITT

[1] The MCID was defined in the PICO as 'seizure freedom one-year post MRgLITT 10% better than conventional surgery'.

	on their non-dominant hemisphere (Bermudez et al 2020) (n=13). (**VERY LOW**) At 12 months follow-up after the first procedure: • One case series of adults and children with mesial temporal lobe epilepsy (Gross et al 2018) reported a rate of seizure freedom (Engel class I) of 48.3% (95% CI 35.9 to 50.8) (n=58). Gross et al 2018 also reported a rate of seizure freedom (Engel class I) of 58.1% (95% CI 43.3 to 71.6) in patients with mesial temporal lobe epilepsy who had mesial temporal sclerosis (n=43) and a rate of seizure freedom (Engel class I) of 20.0% (95% CI 6.3 to 46.0) in patients with mesial temporal lobe epilepsy who did not have mesial temporal sclerosis (n=15). (**VERY LOW**) At 12 months follow-up after the latest procedure (including nine patients who had had repeat procedures): • One case series of adults and children with mesial temporal lobe epilepsy (Gross et al 2018) (n=58) reported a rate of Engel class I seizures of 53.4% (95% CI 40.8 to 65.7), Engel class II seizures of 22.4% (no CI reported), Engel class III seizures of 19.0% (no CI reported) and Engel class IV seizures of 5.2% (no CI reported). In patients with mesial temporal lobe epilepsy who had mesial temporal sclerosis (n=43) Gross et al 2018 reported a rate of Engel class I seizures of 60.5% (95% CI 45.6 to 73.7), Engel class II seizures of 23.2% (no CI reported), Engel class III seizures of 16.3% (no CI reported) and Engel class IV seizures of 0. In patients with mesial temporal lobe epilepsy who did not have mesial temporal sclerosis (n=15) Gross et al 2018 reported a rate of Engel class I seizures of 33.3% (95% CI 15.0 to 58.5), Engel class II seizures of 20.0% (no CI reported), Engel class III seizures of 26.7% (no CI reported) and Engel class IV seizures of 20.0% (no CI reported). **(VERY LOW)** At 12 months follow-up: • One case series of patients with DRE who had mesial temporal lobe epilepsy or mesial temporal sclerosis epilepsy (n=24) (Landazuri et al 2020) reported a rate of Engel class I seizures of 70.8 % (95% CI 48.9 to 87.4), Engel class II seizures of 12.5% (no CI reported), Engel class III seizures of 16.7% (no CI reported) and Engel class IV seizures of 0. (**VERY LOW**) At 24 months after the latest procedure (including nine patients who had had repeat procedures): • One case series of adults and children with mesial temporal lobe epilepsy (Gross et al 2018) (n=58) reported a rate of seizure freedom (Engel class I) of 34.3% (95% CI 19.7 to 49.3). **(VERY LOW)** At 12 to 36 months follow-up: • One SRMA of nine case series of patients with temporal lobe-based seizure pathologic conditions (n=250) (Sanjeet et al 2019) reported a mean incidence of seizure freedom (Engel class IA +/-

	class IB) of 50%, (95% CI 44 to 56) (I^2 =0.00, p=0.78). **(VERY LOW)** *For patients with drug-resistant focal epilepsy due to other specific aetiologies:* At more than six months follow-up: • One SRMA (Wang et al 2020) reported a mean seizure free rate of 62% (95% CI 28 to 91) in a meta-analysis of two case series including patients with focal cortical dysplasia (n=12), a mean seizure free rate of 66% (95% CI 15 to 100) in a meta-analysis of two case series including patients with tuberous sclerosis complex (n=5), and a mean seizure free rate of 40% (95% CI 0 to 90) in a meta-analysis of two case series including patients with periventricular nodular heterotopias (n=5). **(VERY LOW)** At 12 months follow-up: • One case series of patients with DRE who had a range of non-temporal lobe epilepsy aetiologies (specific aetiologies included in this outcome not stated) (n=18) (Landazuri et al 2020) reported a rate of Engel class I seizures of 55.6% (95% CI 30.8 to 78.5), Engel class II seizures of 5.6% (no CI reported), Engel class III seizures of 27.8% (no CI reported) and Engel class IV seizures of 11.1% (no CI reported). **(VERY LOW)** **The six non-comparator studies provided very low certainty evidence that the mean seizure free rate (Engel class I) at follow-up periods of between 7 days and 51 months after MRgLITT ranged from 61% to 65% in patients with drug-resistant focal epilepsy due to mix of aetiologies, from 34% to 71% in patients with drug-resistant focal epilepsy of temporal lobe origin, and from 40% to 66% in patients with drug-resistant focal epilepsy due to range of specific non-temporal lobe epilepsy aetiologies. Between 0% and 15% of patients across the different groups experienced no worthwhile improvement (Engel class IV). No conclusions can be drawn about seizure outcomes in patients undergoing SLAH compared with open resection due to small numbers and lack of significance measures, and no conclusions can be drawn about seizure freedom in relation to the MCID defined in the PICO.**
Neuropsychological outcomes Certainty of evidence: Very low	This outcome is key to patients and their carers because it can help to identify areas of difficulty and improvement in cognitive function and also the relationship between epilepsy and a patient's emotional function.
	Children and adults with refractory focal epilepsy caused by hypothalamic hamartoma unsuitable for neurosurgical resection No evidence was identified for this outcome.
	Children and adults with refractory focal epilepsy when open neurosurgery carries a high risk of serious adverse effects.

	One comparator cohort study and two case series provided evidence on neuropsychological outcomes for people with drug-resistant focal epilepsy with identifiable epileptogenic zones treated with MRgLITT. At 6 months or 1 year follow-up: • One comparator cohort study (Drane et al 2015) (n=58) reported pre-operative mean (SD) score and mean (SD) change in score for three measures of naming or recognition. Follow-up was 6 months for subjects undergoing SLAH and 1 year for subjects undergoing open resection. o For the Boston Naming Test the mean (SD) score and mean (SD) change in score were 70.3 (22.4) and 8.6 (25.7) for subjects undergoing SLAH on their dominant hemisphere; 76.6 (14.5) and -23.6 (17.6) for subjects undergoing open resection on their dominant hemisphere; 85.6 (11.1) and 3.2 (3.7) for subjects undergoing SLAH on their non-dominant hemisphere, and 92.7 (7.0) and 1.9 (4.8) for subjects undergoing open resection on their non-dominant hemisphere. o For the Famous Face Naming Test they were 67.0 (23.6) and 9.4 (12.5) for subjects undergoing SLAH on their dominant hemisphere; 69.9 (21.2) and -28.3 (30.5) for subjects undergoing open resection on their dominant hemisphere; 89.9 (6.0) and 7.6 (12.6) for subjects undergoing SLAH on their non-dominant hemisphere, and 89.7 (6.9) and 1.4 (8.1) for subjects undergoing open resection on their non-dominant hemisphere. The score change for the dominant open resection groups for both naming tests was statistically significantly worse than the other three groups ($p<0.01$). o For the Famous Face Recognition Test the scores were 72.9 (16.7) and 4.2 (5.5) for subjects undergoing SLAH on their dominant hemisphere; 66.1 (15.2) and 0.5 (13.2) for subjects undergoing open resection on their dominant hemisphere; 74.0 (16.6) and 5.0 (4.9) for subjects undergoing SLAH on their non-dominant hemisphere, and 76.0 (18.8) and -9.0 (16.5) for subjects undergoing open resection on their non-dominant hemisphere. The score change for the non-dominant open resection group was statistically significantly worse than the other three groups ($p<0.001$). **(VERY LOW)** • Drane et al 2015 also reported that the number of subjects declining on one or more naming or recognition tasks was 0/19 in the SLAH group and 32/39 in the open resection group ($p < 0.0001$). **(VERY LOW)** At an average 6.4 (+/- 1.5) months (range 5-11 months) follow-up: • One case series (Gross et al 2018) (n=49) reported mean +/-SD (range) pre-op and follow-up scores for RAVLT-learning of 41.8 +/- 10.8 (14 to 65) and 41.9 +/- 11.6 (11 to 59), and for RAVLT-delayed recall of 5.9 +/- 3.9 (0 to 15) and 6.5 +/- 4.1 (0 to 14) (p values not reported, differences not significant). For patients having MRgLITT on their dominant hemisphere (n=20) they

	reported mean +/-SD (range) pre-op and follow-up scores for RAVLT-learning of 37.4 +/- 10.7 (14 to 62) and 35.3 +/- 12.7 (11 to 56), and for RAVLT-delayed recall of 4.6 +/- 3.7 (0 to 13) and 4.2 +/- 3.4 (1 to 12) (p values not reported, differences not significant). For patients having MRgLITT on their non-dominant hemisphere (n=29) they reported mean +/-SD (range) pre-op and follow-up scores for RAVLT-learning of 44.9 +/- 10.0 (33 to 65) and 46.6 +/- 8.3 (22 to 59) (p value not reported, difference not significant), and for RAVLT-delayed recall of 6.6 +/- 3.9 (1 to 15) and 8.2 +/- 3.7 (0 to 14) ($p<0.05$) (higher scores better). **(VERY LOW)** At a mean 8.4 (+/- 3.3) months follow-up: • One case series (Bermudez et al 2020) (n range 6 to 11) reported pre-op and follow-up scores for a range of neuropsychological measures for patients having MRgLITT on their dominant (dom) or non-dominant (non-dom) hemisphere. Higher scores were better for all measures. For the Wechsler memory scale, mean (+/-SD) pre-op and follow-up scores were dom (n=10) 43.6 (+/-13.9) and 41.7 (+/-13.4), and non-dom (n=6) 45.3 (+/-10.9) and 48.8 (+/-3.4). For list learning, mean pre-op and follow-up % learned (+/-SD) was dom (n=10) 57.0% (+/-12.1) and 57.2% (+/-13.1), and non-dom (n=9) 58.7% (+/-18.5) and 66.9% (+/-14.6), and mean pre-op and follow-up % retained was dom (n=10) 47.3% (+/-19.2) and 39.8% (+/-25.9), and non-dom (n=9) 62.0% (+/-21.2) and 73.2% (+/-14.6). For the Brief Visual Memory Test-revised, the mean pre-op and follow-up total T-score (+/-SD) was dom (n=8) 35.7 (+/-10.6) and 38.3 (+/-13.9), and non-dom (n=8) 31.8 (+/-12.9) and 35.9 (+/-12.1). For Naming, the mean pre-op and follow-up % correct (+/-SD) was dom (n=11) 63.3% (+/-14.7) and 60.5% (+/-20.4), and non-dom (n=10) 68.9% (+/-16.8) and 72.2% (+/-16.6). For the Controlled Oral Word Association Test (verbal fluency), mean pre-op and follow-up T scores (+/-SD) were dom (n=11) Phonemic T-score 41.1 (+/-11.8) and 44.9 (+/-12.5), and Semantic T-score 40.6 (+/-11.8) and 39.4 (+/-9.9), and non-dom (n=9) Phonemic T score 42.4 (+/-18.0) and 50.3 (+/-10.7), and Semantic T score 44.0 (+/-9.8) and 39.8 (+/-9.5). For the Trails A (processing speed) test, mean pre-op and follow-up T scores (+/-SD) were dom (n=9) 35.8 (+/-10.9) and 40.0 (+/-10.3), and non-dom (n=6) 32.8 (+/-4.0) and 46.2 (+/-8.7). For the grooved pegboard test (fine motor dexterity), the mean pre-op and follow-up T scores (+/-SD) were dom (n=11) 36.5 (+/-8.8) and 38.9 (+/-8.7), and non-dom (n=7) 36.0 (+/-9.2) and 41.7 (+/-10.1). **(VERY LOW)** **One comparator cohort study provided very low certainty evidence that subjects undergoing open resection on their dominant hemisphere had significantly worse performance on naming tests at follow-up than subjects undergoing SLAH on their dominant hemisphere or SLAH or open resection on their non-dominant hemisphere, and that subjects undergoing open resection on their non-dominant hemisphere had significantly worse performance on a facial recognition test at follow-up than subjects undergoing SLAH on their non-dominant hemisphere or SLAH or open resection on their dominant hemisphere. It also**

	provided very low certainty evidence that significantly more subjects undergoing open resection experienced a decline in any naming or recognition tasks than subjects undergoing SLAH, among whom none experienced a decline. Two non-comparator studies provided very low certainty evidence that auditory verbal learning and delayed recall were not significantly different before and after MRgLITT for all patients with drug-resistant focal epilepsy of temporal lobe origin, and for patients with drug-resistant focal epilepsy of temporal lobe origin who had MRgLITT on their dominant hemisphere. There was very low certainty evidence that auditory verbal learning delayed recall was significantly better after MRgLITT for patients with drug-resistant focal epilepsy of temporal lobe origin who had MRgLITT on their non-dominant hemisphere. It is not possible to draw conclusions about the evidence on any other neuropsychological measures reported due to small numbers and lack of significance measures.
Quality of life Certainty of evidence: Very low	Quality of life is important to patients because its holistic evaluation incorporating contributing factors (such as emotional well-being, social and physical functioning, medication effects and role limitations) reflects impact upon the patient's life and its improvement is a marker of successful treatment
	Children and adults with refractory focal epilepsy caused by hypothalamic hamartoma unsuitable for neurosurgical resection **No evidence was identified for this outcome.**
	Children and adults with refractory focal epilepsy when open neurosurgery carries a high risk of serious adverse effects. One case series provided evidence on quality of life for patients having MRgLITT for drug-resistant focal epilepsy due to a range of aetiologies (these included temporal lobe epilepsy and other aetiologies, but the specific aetiologies for those included in this outcome were not stated), using the QOLIE-31 [2] score (higher score better). At latest follow-up (follow-up period not stated): • One case series (Landazuri et al 2020) (n=29) reported the median total QOLIE-31 score. At baseline this was 51.7 (range 8.7 to 77.3) and at latest follow-up it was 65.8 (range not stated) (p=0.2173). They also reported the median improvement in QOLIE subscores (p value) from baseline to latest follow-up to be: seizure worry: +15 (p=0.0219), emotional wellbeing: +8 (not significant), energy/fatigue: +5 (not significant), cognitive function: +7 (not significant) and social functioning: +15 (p=0.0175). **(VERY LOW)** **This study provided very low certainty evidence that compared to baseline, there was a significant improvement in seizure worry and social functioning subscores, but no significant change in emotional wellbeing, energy/fatigue or cognitive function subscores, and no significant improvement in total QOLIE-31 score at an unspecified follow-up period for patients having**

	MRgLITT for drug-resistant focal epilepsy due to a range of aetiologies.
Important outcomes	
Need for medical therapy Certainty of evidence: Very low	**Assessing reduction or discontinuation in medical therapy following MRgLITT is important to patients because it is a marker of the effectiveness of the intervention, especially considering that many patients will have previously been taking multiple medications with sub-optimal control of their epilepsy and potentially with side effects.**
	Children and adults with refractory focal epilepsy caused by hypothalamic hamartoma unsuitable for neurosurgical resection At an unspecified follow-up period: • One case series (Curry et al 2018) (n=71) reported that 12% of patients were free from seizures and free of antiepileptic medicines (no CI reported). (**VERY LOW**) **This study provided very low certainty evidence that 12% of patients with drug-resistant focal epilepsy who had hypothalamic hamartoma were free from seizures and free of antiepileptic medicines at an unspecified follow-up period after MRgLITT.**
	Children and adults with refractory focal epilepsy when open neurosurgery carries a high risk of serious adverse effects. No evidence was identified for this outcome.
Hospitalisations Certainty of evidence: Very low	Patients may require hospitalisation for treatment of seizures and their aftermath to prevent consequences such as physical injury, cognitive damage and psychiatric complications. However, a reduction in number and length of hospitalisations is important to patients and their carers as it indicates that their treatment has been successful in reducing severe seizure activity.
	Children and adults with refractory focal epilepsy caused by hypothalamic hamartoma unsuitable for neurosurgical resection. No evidence was identified for this outcome.
	Children and adults with refractory focal epilepsy when open neurosurgery carries a high risk of serious adverse effects. One study provided evidence on rehospitalisation. At up to 90 days after the procedure: • One study (Landazuri et al 2020) (n included for this outcome not reported, total n=42) reported that one patient had been rehospitalised within 90 days of the procedure. The total study population included subjects with a range of aetiologies, but the specific aetiologies included in this outcome were not defined. **(VERY LOW)**

	This study provided very low certainty evidence that one patient out of a total cohort of up to 42 was rehospitalised within 90 days of having MRgLITT.
Cognitive development in children Certainty of evidence: Not applicable	This outcome is key to patients and their carers because an improvement in cognitive learning can increase independence, ability to learn and problem-solve and enhance confidence during formative years.
	Children and adults with refractory focal epilepsy caused by hypothalamic hamartoma unsuitable for neurosurgical resection. No evidence was identified for this outcome.
	Children and adults with refractory focal epilepsy when open neurosurgery carries a high risk of serious adverse effects. No evidence was identified for this outcome.
Safety	
Complications from procedure Certainty of evidence: Very low	Procedural complications are important to patients because they may be irreversible, can be serious and need be considered to inform treatment choices.
	Children and adults with refractory focal epilepsy caused by hypothalamic hamartoma unsuitable for neurosurgical resection. In the immediate post-operative period: • One case series (Xu et al 2018) (n=18) reported neurological deficits in seven (39%) subjects (no CI reported), consisting of strength deficit in five; unilateral Horner's syndrome in one; and both strength deficit and unilateral Horner's syndrome in one. (**VERY LOW**) At mean 6.3 (+/- 4.8 months) follow-up: • One case series (Xu et al 2018) (n=18) reported neurological deficits in five (28%) subjects, two of which were new deficits; short-term memory deficits in five (28%) subjects, three of which were new; newly diagnosed hypothyroidism in two (11%) subjects, and weight gain from increased appetite in four (22%) subjects (no CI reported). (**VERY LOW**) At mean >17.5 months (+/- 7.5 months) follow-up: • One case series (Xu et al 2018) (n=18) reported persistent neurological deficits in four (22%) subjects, hypothyroidism in two (11%) subjects, short-term memory issues in four (22%) subjects, and persistent weight gain in four (22%) subjects (no CI reported). (**VERY LOW**) At an unspecified follow-up period: • One case series (Curry et al 2018) (n=71) reported two episodes of persistent complications (one worsening diabetes insipidus, and one severe deficit in short-term memory which did not resolve) and 16 episodes of complications which resolved (four delayed wound healing, three single episodes of hyponatremia, and nine

	temporary increases in non-gelastic seizures that resolved at four months post-surgery). (**VERY LOW**) **These studies provided very low certainty evidence that both short-term and persistent complications were experienced by patients following MRgLITT. These included persistent neurological deficits, short-term memory deficits and endocrine problems. However the proportion of patients not affected by complications in the studies was not clear and the type and frequency of complications reported varied between studies**.
	Children and adults with refractory focal epilepsy when open neurosurgery carries a high risk of serious adverse effects. Five studies (three SRMAs of between seven and thirteen case series, and two case series) provided evidence on complications from the procedure. *For patients with drug-resistant focal epilepsy due to a mix of aetiologies:* At an unspecified follow-up period: • Two SRMAs (Wang et al 2020, Xue et al 2018) (n= not stated, n=101) reported post-operative complications. Xue et al 2018 reported a pooled rate of post-operative complications of 24% (95% CI 16 to 32) (range across studies 15% to 43%) (I^2=0%; p=0.629). At more than six months follow-up Wang et al reported a rate of complications of 7% (95% CI 4 to 11), a total of 27 complications. **(VERY LOW)** At 12 months follow-up: • One case series (Landazuri et al 2020) (n=60) reported that 5/60 (8.3%) patients had procedure-related adverse events, of which four were 'not serious' and one was 'serious'. **(VERY LOW)** *For patients with drug-resistant focal epilepsy of temporal lobe origin:* At 12 months follow-up: • One case series (Gross et al 2018) (n=58) reported that 5/58 (8.6%) patients had a visual field deficit, one of which (1.7%) was persistent and symptomatic. **(VERY LOW)** At a median 22.4 months (range 7-70 months) follow-up: • One SRMA (Sanjeet et al 2019) (n=207) reported an overall complication rate of 20% (95% CI 14 to 26) (I^2 =0.00, p=0.63). **(VERY LOW)** **These studies provided very low certainty evidence that the rate of complications recorded at between more than six months and a median 22.4 months follow-up after MRgLITT was between 7% and 24%.**
Re-operation rate	Rarely, if open neurosurgery has failed re-operating may be considered. However, reoperations can lead to an increased rate of permanent neurological deficits, overall surgical complications, infection and visual field deficits. This is an important outcome for

Certainty of evidence: Very low	patients as the risks of reoperation can adversely impact their quality of life and function.
	Children and adults with refractory focal epilepsy caused by hypothalamic hamartoma unsuitable for neurosurgical resection. **This outcome was not included in the PICO for this review.**
	Children and adults with refractory focal epilepsy when open neurosurgery carries a high risk of serious adverse effects. One SRMA of seven case series of patients with temporal lobe-based seizure pathologic conditions provided evidence on re-operations. At a median 22.4 months (range 7-70 months) follow-up: • One SRMA (Sanjeet et al 2019) (n=184) reported a mean re-operation rate of 15% (95% CI 9 to 22) (I^2 =19.87, p=0.28). The re-operations reported included repeat LITT and anterior temporal lobectomy. **(VERY LOW)** **This study provides very low certainty evidence that around 15% of patients require re-operation up to a median of 22.4 months after MRgLITT.**

Seizure classifications (Wieser et al 2001)

[a] Engel seizure classification: *Class I: Free of disabling seizures* (IA: Completely seizure-free since surgery; IB: Non disabling simple partial seizures only since surgery; IC: Some disabling seizures after surgery, but free of disabling seizures for at least 2 years; ID: Generalized convulsions with antiepileptic drug withdrawal only): *Class II: Rare disabling seizures* ("almost seizure-free") (IIA: Initially free of disabling seizures but has rare seizures now; IIB: Rare disabling seizures since surgery; IIC: More than rare disabling seizures after surgery, but rare seizures for at least 2 years; IID: Nocturnal seizures only) *Class III: Worthwhile improvement* (IIIA: Worthwhile seizure reduction; IIIB: Prolonged seizure-free intervals amounting to greater than half the follow-up period, but not less than 2 years): *Class IV: No worthwhile improvement* (IVA: Significant seizure reduction; IVB: No appreciable change; IVC: Seizures worse

[b] ILAE: International League Against Epilepsy; Classification 1: Completely seizure free, no auras; 2: Only auras, no other seizures; 3: one to three seizure days per year: +/- auras; 4: Four seizure days per year to 50% reduction of baseline seizure days; ± auras; 5: Less than 50% reduction of baseline seizure days to 100% increase of baseline seizure days; ± auras; 6: More than 100% increase of baseline seizure days; ± auras

Abbreviations: CI: Confidence Intervals; Dom: language dominant hemisphere; DRE: drug-resistant epilepsy; ; ILAE: International League Against Epilepsy; MRgLITT: MR-guided laser interstitial thermal therapy; Non-dom: non-dominant hemisphere; RAVLT: Rey auditory verbal learning test; SD: standard deviation SRMA: systematic review and meta-analysis;

In adults and children with drug-resistant focal epilepsy who have hypothalamic hamartoma what is the cost effectiveness of MRgLITT compared with continued medical therapy, and in adults and children with drug-resistant focal epilepsy who have identifiable epileptogenic zones what is the cost effectiveness of MRgLITT compared with open neurosurgical resection or continued medical therapy alone?

Outcome	Evidence statement

Cost Effectiveness	Children and adults with refractory focal epilepsy caused by hypothalamic hamartoma unsuitable for neurosurgical resection. No evidence was identified for cost effectiveness.
	Children and adults with refractory focal epilepsy when open neurosurgery carries a high risk of serious adverse effects. One study (Widjaja et al 2019) compared cost-utility for a hypothetical cohort of adults with temporal lobe epilepsy undergoing MRgLITT or epilepsy surgery. Model inputs were taken from studies published between 1994 and 2019; the time period for costs used was not stated. • One cost-utility study estimated that adults undergoing MRgLITT for temporal lobe epilepsy gained 24.7 QALYs at a cost of $165,3036, while adults undergoing epilepsy surgery gained 24.62 QALYs at a cost of $157,482. The base case incremental cost effectiveness ratio of MRgLITT compared with epilepsy surgery was $94,350 per QALY (costs in Canadian dollars). Sensitivity analyses carried out indicated that surgery was the preferred strategy in more than 50% of the sensitivity analysis iterations. **This study provides evidence that epilepsy surgery may be more cost-effective than MRgLITT in adults with temporal lobe epilepsy.**
Abbreviations: MRgLITT: MR-guided laser interstitial thermal therapy; QALY: quality-adjusted life year;	

From the evidence selected, are there any subgroups of people that may benefit from MRgLITT more than the wider population of interest?

Outcome	Evidence statement
Subgroups	Children and adults with refractory focal epilepsy caused by hypothalamic hamartoma unsuitable for neurosurgical resection. No evidence was identified regarding any subgroups of patients that would benefit more from treatment with MR-guided LITT.
	Children and adults with refractory focal epilepsy when open neurosurgery carries a high risk of serious adverse effects. One study (Drane et al 2015) compared neuropsychological outcomes in adults undergoing SLAH on their language dominant or their non-dominant hemisphere. The dominant hemisphere group had significantly worse performance on naming tasks at baseline. No significant differences were reported between these two groups in change in naming or recognition scores at 6 months follow-up. Five studies (Bermudez et al 2020, Gross et al 2018, Landazuri et al 2020, Sanjeet et al 2019, Wang et al 2020) reported outcomes for patients with specified types of lesions. However none carried out direct comparisons between groups of any of the outcomes reported.

	Three studies (Gross et al 2018, Wang et al 2020, Xue et al 2018) included both adults and children, one (Drane et al 2015) included adults only, and the remainder did not state the age range of included subjects. No studies reported outcomes by age group. **No significant difference was reported in change in performance of naming or recognition tasks at 6 months follow-up between subjects undergoing SLAH on their language dominant or non-dominant hemisphere. No other evidence was identified on subgroups of people that may benefit from MR-guided LITT more than the wider population of interest.**
Abbreviations: SLAH: stereotactic laser amygdalohippocampotomy	

Patient Impact Summary

The condition has the following impacts on the patient's everyday life:

- **mobility:** Patients can have moderate to severe problems with mobilising as a direct consequence of epilepsy. Anti-epileptic drugs (AEDs) can also cause issues with mobility and walking (or both are also applicable). Patients are unable to drive.
- **ability to provide self-care:** Patients can have moderate to severe problems with providing self-care as when incapacitated from having a seizure they are unable to function and take care of their own personal welfare; i.e. when self-medicating there can be confusion in remembering when, or what medication they have taken post seizure.
- **undertaking usual activities:** Patients can have moderate to severe problems in doing their usual activities due to disease severity, neurological symptoms, weakness and fatigue.
- **experience of pain/discomfort:** Patients may experience moderate to severe pain or discomfort through the disease course, and as a result of injuries caused during seizures.
- **experience of anxiety/depression:** Patients can experience moderate to severe anxiety and/or depression due to the life-changing and uncertain nature of diagnosis, treatment and changes to lifestyle. Patients Wellbeing is severely impacted when they experience anxiety /depression which may require clinical intervention from mental health care professionals.

This document was written with assistance from the Policy Working Group's PPV and their lived experience.

Further details of impact upon patients:

Patients have often trialled AEDs with limited success, and may experience cerebral injuries, long-term disabilities, and psychological, psychiatric, financial and social comorbidities. These factors coupled with the limitations in physical activity can have a profoundly negative effect on mental health. Severe anxiety

and depression are often experienced by patients during this uncertain time. This has contributed to the increased risk of suicide in this patient group. Patients are not always able to reach their full educational/employment potential due to the frequency of their symptoms, and in particular employers can find it difficult in making a reasonable adjustment prescriptive, subsequently finding right employment is problematic - voluntary work is often the only option open to them, which in turn has financial implications.

Also living independently is often challenging and cannot always be achieved due to risk of injuring themselves and of death related to seizures, and it can be difficult accessing appropriate outside support to help facilitate their requirements. This puts additional strain on carers (see below). Lifestyle choices can be limited due to their vulnerability and their ability to read situations can be an issue.

Further details of impact upon carers:

As described above patients can experience a wide range of physical and mental symptoms. Pain, limited mobility and increasing anxiety and depression can limit the ability to carry out activities of daily living and patients may depend upon carers to assist with personal care, mobilising, shopping and running errands. Furthermore, carers may provide assistance for attending hospital appointments and treatment.

Carers will also often provide emotional support at this time in a patient's life. Often relatives perform the caring role and the emotional toll of such a serious diagnosis can impact upon carers as well as the patient in this situation. Due to the unpredictable nature of the seizures the patient may need continuous care, where the carer has to manage the condition through observing and re-engaging with the patient post seizure to enable the patient to recover and regain awareness of the surroundings. The responsibility that falls to the carer having to manage the patient's condition 24/7 will inevitably have a wider impact on their immediate and extended family. A good understanding of the condition is not well recognised and therefore accessing the right healthcare professionals with the subject matter expertise can be difficult.

Considerations from review by Rare Disease Advisory Group
Not applicable

Pharmaceutical considerations
Not applicable

Considerations from review by National Programme of Care
The proposition received the full support of the Trauma PoC on the 8th June 2022