NHS England Evidence Review:

MR-guided laser interstitial thermal therapy for children and adults with refractory focal epilepsy when open neurosurgery carries a high risk of serious adverse effects

NHS England URN: 2006b

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Drafted: January 2021

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Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of MR-guided laser interstitial thermal therapy (MRgLITT) compared to open neurosurgical resection or continued medical therapy alone for children and adults with refractory focal epilepsy when open neurosurgery carries a high risk of serious adverse effects. Drug-resistant or refractory epilepsy can cause significant impairment of quality of life. Patients are at risk of recurrent physical and cerebral injury from seizures, status epilepticus (prolonged seizures), sudden death in epilepsy, other causes of fatality and psychological, psychiatric, financial and social comorbidities. Patients will have tried various anti-epileptic medications, often with adverse effects, and may have had frequent hospitalisations.

Causes of refractory focal epilepsy may include hippocampal sclerosis located in the medial temporal lobe, cortical dysplasia, heterotopic nodules, low grade glioneuronal tumours, scar tissue from brain trauma, meningitis or stroke, malformations and other lesions. In those who have refractory focal epilepsy and a well-defined epileptogenic zone, open neurosurgical removal or ablation of this part of the brain can be curative. However, for some patients, open neurosurgery can carry a high risk of causing severe neurological deficit.

MRgLITT is proposed as a treatment for refractory focal epilepsy which carries less risk than open neurosurgery. It involves the identification of the epileptogenic lesion on magnetic resonance imaging (MRI), and the insertion of a fine fibreoptic laser catheter into the target area through a burr hole in the skull. The procedure is carried out under continuous real-time MRI scanning to allow visualisation of the exact target area and the surrounding tissue, and to monitor the temperature in the brain during the procedure. Laser energy is applied with the aim of ablating the target tissue while causing minimal damage to the surrounding area.

In addition to considering the clinical effectiveness, safety and cost effectiveness of MRgLITT for drug-resistant focal epilepsy, the scope of this review also included the identification of possible subgroups of patients within the included studies who might benefit from treatment with MRgLITT more than others.

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2. Executive summary of the review

Eight studies were included in the evidence review (Bermudez et al 2020, Drane et al 2015, Gross et al 2018, Landazuri et al 2020, Sanjeet et al 2019, Wang et al 2020, Widjaja et al 2019, Xue et al 2018).

Three were systematic review and meta-analyses (SRMAs) (Sanjeet et al 2019, Wang et al 2020, Xue et al 2018) which included between nine and sixteen case series of between 189 and 414 patients who had MR-guided laser interstitial thermal therapy (MRgLITT).

One was a study comparing cohorts undergoing stereotactic laser amygdalohippocampotomy (SLAH) or open resection (Drane et al 2015).

Two included papers were retrospective case series; Bermudez et al 2020 included 26 patients and Gross et al 2018 included 58 patients. Landazuri et al 2020 was a case series which included prospectively collected data on 42 patients.

Widjaja et al 2019 was a cost-utility study comparing MRgLITT and surgery in patients with temporal lobe epilepsy. Three studies (Gross et al 2018, Wang et al 2020, Xue et al 2018) included both adults and children, Drane et al 2015 and Widjaja et al 2019 included adults only, and the remaining studies reported the mean age of subjects to be between 35 and 42 years but did not report the age range. Studies reported outcomes at timepoints ranging from six months to a maximum of 51 months after MRgLITT.

Research Question 1:

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

Critical outcomes

The critical outcomes for decision making are seizure freedom, neuropsychological outcomes and quality of life.

The certainty of the evidence for all critical outcomes was very low when assessed using modified GRADE.

Seizure freedom

In total 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 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 seven days and 51 months after the procedure and was defined using the Engel classification[1] in six studies (Drane et

[1] 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

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, the SRMA by 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)). At 12 months follow-up 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).

At between seven days and 51 months follow-up (Xue et al 2018), 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)), and 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)).

For patients with drug-resistant focal epilepsy of temporal lobe origin:

At six months follow-up a 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 small numbers and lack of statistical measures mean that no conclusions can be drawn about these seizure outcomes compared with the minimum clinically important difference (MCID) threshold defined in the PICO[2].

At more than six months follow-up, the SRMA by Wang et al 2020 (n=266) reported a mean seizure free rate (Engel class I) of 59% (95% CI 53 to 65), (I^2 =0.00, (p=0.83)). Bermudez et al 2020 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 (n=13) at mean 8.3 (+/-1.27) months follow-up. Bermudez et al 2020 also 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 on their non-dominant hemisphere (n=13) at mean 8.5 (+/-4.6) months follow-up.

At 12 months follow-up after the first procedure, one case series of patients 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

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;

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

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).

In the same cohort, at 12 months follow-up after the latest procedure (including nine patients who had had repeat procedures), 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).

At 12 months follow-up, in patients with 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.

At 24 months after the latest procedure (including nine patients who had had repeat procedures) in patients 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). At 12 to 36 months follow-up the SRMA of patients with temporal lobe-based seizure pathologic conditions (n=250) by 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).

For patients with drug-resistant focal epilepsy due to other specific aetiologies:

The SRMA by Wang et al 2020 reported a rate of seizure freedom (Engel class I) at more than six months after MRgLITT in patients with focal cortical dysplasia (n=12) of 62% (95% CI 28 to 91), in patients with tuberous sclerosis complex (n=5) of 66% (95% CI 15 to 100), and in patients with periventricular nodular heterotopias (n=5) of 40% (95% CI 0 to 90). In a group of patients with drug-resistant focal epilepsy due to a range of non-temporal lobe epilepsy aetiologies (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) at 12 months follow-up.

Neuropsychological outcomes[3]

One comparator cohort study and two case series provided evidence relating to neuropsychological outcomes for people with drug-resistant focal epilepsy of temporal lobe origin treated with MRgLITT.

One comparator cohort study (Drane et al 2015) (n=58) reported three measures of naming or recognition at six months follow-up for subjects undergoing SLAH and at one year follow-up for subjects undergoing open resection (higher score better for all measures). Outcomes

[3] These outcomes have been presented in tables at the request of the PWG.

were reported for subjects undergoing the intervention on the language dominant (SLAH n=10, open resection n=22) or non-dominant (SLAH n=9, open resection n=17) hemisphere (Table ES1). There were significant differences between groups on both naming tests at baseline (the non-dominant groups scoring significantly better than the dominant groups, p<0.001). 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), and the score change for the non-dominant open resection group was statistically significantly worse than the other three groups (p<0.001). **(VERY LOW)**

Table A: Neuropsychological outcomes (Drane et al 2015)

	Mean pre-op score (SD)	Mean change in score at follow-up (SD)
Boston Naming Test		
Dom SLAH (n=10)	70.3 (22.4)	8.6 (25.7)
Dom open resection (n=22)	76.6 (14.5)	-23.6* (17.6)
Non-dom SLAH (n=9)	85.6 (11.1)	3.2 (3.7)
Non-dom open resection (n=17)	92.7 (7.0)	1.9 (4.8)
Famous Face Naming Test		
Dom SLAH (n=10)	67.0 (23.6)	9.4 (12.5)
Dom open resection (n=22)	69.9 (21.2)	-28.3* (30.5)
Non-dom SLAH (n=9)	89.9 (6.0)	7.6 (12.6)
Non-dom open resection (n=17)	89.7 (6.9)	1.4 (8.1)
Famous face recognition		
Dom SLAH (n=10)	72.9 (16.7)	4.2 (5.5)
Dom open resection (n=22)	66.1 (15.2)	0.5 (13.2)
Non-dom SLAH (n=9)	74.0 (16.6)	5.0 (4.9)
Non-dom open resection (n=17)	76.0 (18.8)	-9.0** (16.5)
Abbreviations: Dom: dominant language hemisphere; Non-dom: non-dominant hemisphere; SLAH: stereotactic laser amygdalohippocampotomy		

*significantly different from other 3 groups, p<0.01
**significantly different from other 3 groups, p<0.001

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, Gross et al 2018 (n=49) reported pre-op and follow-up scores for the Rey auditory verbal learning test (RAVLT) - learning and RAVLT-delayed recall (Table ES2). For patients having MRgLITT on their non-dominant hemisphere the mean follow-up score for RAVLT -delayed recall was statistically significantly better than the mean pre-op score (p<0.05). None of the other score differences were statistically significantly different. **(VERY LOW)**

Table B: Neuropsychological outcomes (Gross et al 2018)

	Mean pre-op score +/-SD (range)	Mean follow-up score +/-SD (range)
RAVLT-learning (all patients, n=49)	41.8 +/- 10.8 (14 to 65)	41.9 +/- 11.6 (11 to 59) *
RAVLT-delayed recall (all patients, n=49)	5.9 +/- 3.9 (0 to 15)	6.5 +/- 4.1 (0 to 14) *
RAVLT-learning (dom, n=20)	37.4 +/- 10.7 (14 to 62)	35.3 +/- 12.7 (11 to 56) *
RAVLT-delayed recall (dom, n=20)	4.6 +/- 3.7 (0 to 13)	4.2 +/- 3.4 (1 to 12) *
RAVLT-learning (non-dom, n=29)	44.9 +/- 10.0 (33 to 65)	46.6 +/- 8.3 (22 to 59) *

RAVLT-delayed recall (non-dom, n=29)	6.6 +/- 3.9 (1 to 15)	8.2 +/- 3.7 (0 to 14) **
Abbreviations: Dom: dominant language hemisphere; Non-dom: non-dominant hemisphere; RAVLT: Rey auditory verbal learning test		

*p values for pre-op to follow-up difference not reported, not statistically significant
**pre-op to follow-up difference p<0.05

At a mean 8.4 (+/- 3.3) months follow-up, 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 or non-dominant hemisphere (Table ES3). Higher scores were better for all measures. No significance measures were reported for any outcomes. **(VERY LOW)**

Table C: Neuropsychological outcomes (Bermudez et al 2020)

	Mean pre-op score (SD)	Mean follow-up score (SD)
Wechsler memory scale		
Dom (n=10)	43.6 (13.9)	41.7 (13.4)
Non-dom (n=6)	45.3 (10.9)	48.8 (3.4)
List learning (% learned)		
Dom (n=10)	57.0% (12.1)	57.2% (13.1)
Non-dom (n=9)	58.7% (18.5)	66.9% (14.6)
List learning retention (% retained)		
Dom (n=10)	47.3% (19.2)	39.8% (25.9)
Non-dom (n=9)	62.0% (21.2)	73.2% (14.6)
BVMT-R (visual memory) total T-score		
Dom (n=8)	35.7 (10.6)	38.3 (13.9)
Non-dom (n=8)	31.8 (12.9)	35.9 (12.1)
Naming (% correct)		
Dom (n=11)	63.3% (14.7)	60.5% (20.4)
Non-dom (n=10)	68.9% (16.8)	72.2% (16.6)
COWAT (verbal fluency) phonemic (eg. words beginning with a specified letter) T-score		
Dom (n=11)	41.1 (11.8)	44.9 (12.5)
Non-dom (n=9)	42.4 (18.0)	50.3 (10.7)
COWAT (verbal fluency) semantic (eg. types of objects) T-score		
Dom (n=11)	40.6 (11.8)	39.4 (9.9)
Non-dom (n=9)	44.0 (9.8)	39.8 (9.5)
Trails A (processing speed) T score		
Dom (n=9)	35.8 (10.9)	40.0 (10.3
Non-dom: (n=6)	32.8 (4.0)	46.2 (8.7)
Grooved pegboard test (fine motor dexterity)		
Dom (n=11)	36.5 (8.8)	38.9 (8.7)
Non-dom (n=7)	36.0 (9.2)	41.7 (10.1)
Abbreviations: COWAT: Controlled Oral Word Association Test; Dom: dominant language hemisphere; Non-dom: non-dominant hemisphere;		

Quality of life

One case series provided evidence on quality of life using the QOLIE-31[4] score in patients with 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) (Landazuri et al 2020) (n=29) (higher score better). At baseline the median total QOLIE-31 score was 51.7 (range 8.7 to 77.3) and at latest follow-up (duration of follow-up not stated) 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).

Important outcomes

The important outcomes for decision making are need for medical therapy, hospitalisations and cognitive development in children.

The certainty of the evidence for all important outcomes was very low when assessed using modified GRADE.

Need for medical therapy

No evidence was identified for this outcome.

Hospitalisations

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.

Cognitive development in children

No evidence was identified for this outcome.

Research Question 2

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

The safety outcomes for decision making are complications from the procedure and re-operation rate.

The certainty of the evidence for all safety outcomes was very low when assessed using modified GRADE.

[4] The QOLIE-31 includes 39 items in 6 sections: energy, emotional wellbeing, activities/ social, cognitive function, seizure worry, effects of medication; as well as two items about overall QOL and overall health.

Complications from the procedure

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) reported post-operative complications. Xue et al 2018 (n=101) 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 6 months follow-up (actual follow-up not stated), Wang et al (n= not stated) reported a rate of complications of 7% (95% CI 4 to 11), a total of 27 complications.

At 12 months follow-up, 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'.

For patients with drug-resistant focal epilepsy of temporal lobe origin:

At 12 months follow-up, Gross et al 2018 (n=58) reported 5/58 (8.6%) patients had a visual field deficit, one of which (1.7%) was persistent and symptomatic. At a median 22.4 months (range 7-70 months) follow-up the SRMA by 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).

Re-operation rate

At a median 22.4 months (range 7-70 months) follow-up, the SRMA by 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) among patients with epilepsy of temporal lobe origin. The re-operations reported included repeat LITT and anterior temporal lobectomy.

Research Question 3

3. 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?

One cost-utility study provided evidence on cost effectiveness in a hypothetical cohort of adults (mean age 35.8 years +/- 1.2 years) with temporal lobe epilepsy undergoing MRgLITT or surgery. The outcomes reported were costs, quality-adjusted life years (QALYs) and incremental cost effectiveness ratio (ICER). The analysis was from the Canadian healthcare payer perspective and costs were in Canadian dollars. Model inputs were taken from studies published between 1994 and 2019; the time period for costs used was not stated.

Costs

Widjaja et al 2019 reported that the cost of MRgLITT was $165,303 and of surgery was $157,482.

QALYs

Widjaja et al 2019 reported that the QALYs gained were 24.7 for patients undergoing MRgLITT and 24.62 for patients undergoing surgery.

ICER

Widjaja et al 2019 reported that the base case ICER for MRgLITT compared with surgery was $94,350 per QALY, and that surgery remained the preferred option in the majority of sensitivity analyses.

Research Question 4

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

No evidence was identified on any subgroups of patients that may benefit from MRgLITT more than the wider population of interest

Limitations

One comparator cohort study compared neuropsychological outcomes for patients undergoing MRgLITT at six months follow-up with patients undergoing open neurosurgical resection at one year follow-up. It is unclear whether this difference in follow-up had any effect on the outcomes reported. There were no comparative studies which reported other clinical effectiveness or safety outcomes of MRgLITT compared to open neurosurgical resection or continued medical therapy alone for adults and children with drug-resistant focal epilepsy who have identifiable epileptogenic zones. Factors relating to the design and conduct of the included studies meant that all were at high risk of bias, and certainty about the evidence for all critical and important outcomes was very low when assessed using modified GRADE.

All studies provided limited demographic and/or clinical information about the subjects. The comparator study, one SRMA and one case series reported that they included prospectively collected data, and in the remaining four studies (two SRMAs and two case series) the evidence included was retrospective. Duration of follow-up was not clearly stated for all outcomes but ranged from six months to a maximum of 51 months, and all three case series reported some loss to follow-up. It is unclear to what extent the evidence identified relates to children; two SRMAs and one case series included both adults and children, the comparator study and the cost-utility study included adults only, and the other three studies did not state whether or not children were included. Two SRMAs considered that their included studies had a high risk of bias; the third included only studies which scored above a defined threshold on the MINORS (methodological index for nonrandomised studies) scale, reducing the risk of bias.

The cost utility study compared adults with temporal lobe epilepsy undergoing MRgLITT or surgery but the outcomes data was taken from different studies and it was unclear how comparable the populations were. Some MRgLITT outcomes used in the model were based on estimates due to a lack of data. The analyses were from the Canadian healthcare payer perspective and it is unclear how generalisable this is to the NHS setting. Model inputs were taken from studies published between 1994 and 2019; the time period for costs used was not stated.

Conclusion

This review included three SRMAs including between nine and sixteen case series, one comparator cohort study, three case series two of which were retrospective and one prospective and one cost-utility study.

Compared to baseline, all studies reported improvements in seizure outcomes at follow-up periods from seven days to a maximum of 51 months, for some patients with drug-resistant focal epilepsy due to a variety of aetiologies in whom open neurosurgery carries a high risk of adverse effects. The proportion who were reported to be seizure free ranged from 20% to 71%, depending on the aetiology and duration of follow-up. One study compared MRgLITT with open neurosurgical resection (Drane et al 2015) but the small numbers and lack of statistical measures mean that no conclusions can be drawn about the seizure outcomes compared with the minimum clinically important difference (MCID) threshold defined in the PICO.

The comparator study and two case series also reported neuropsychological outcomes. Significantly worse naming and recognition outcomes were reported in some subjects undergoing open resection compared with those undergoing SLAH. One case series reported a significant improvement in one learning outcome and no significant differences in other learning and recall outcomes at follow-up after MRgLITT.

One case series reported a significant improvement in two quality of life subscores after MRgLITT with no change in the overall quality of life score.

Five studies reported a range of complications following the procedure and one SRMA reported a re-operation rate of 15%. No evidence was identified in relation to need for medical therapy or cognitive development in children.

The comparator study found no significant difference in neuropsychological outcomes between patients undergoing SLAH on their language dominant or their non-dominant hemisphere. There was no evidence on any other subgroups who may benefit from MRgLITT more than the general population of interest.

The cost-utility study reported that surgery was more cost effective than MRgLITT for adults with temporal lobe epilepsy.

The studies were all at risk of bias, limited details were provided about the study subjects included, duration of follow-up was not always clearly stated and all three case series reported loss to follow-up. They therefore provide very low certainty evidence that MRgLITT improves outcomes for children and adults with refractory focal epilepsy in whom open neurosurgery carries a high risk of serious adverse effects, and that neuropsychological outcomes are significantly worse in those undergoing open neurosurgery compared with MRgLITT. The evidence on cost effectiveness should be interpreted with caution due to methodological problems with this study.

3. Methodology

Review questions

The review questions for this evidence review are:

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

2. In adults and children with drug-resistant focal epilepsy with identifiable epileptogenic zones, what is the safety of MRgLITT compared with open neurosurgical resection or continued medical therapy alone?

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

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

See Appendix A for the full review protocol.

Review process

The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2019).

The searches for evidence were informed by the PICO document and were conducted on 19th November 2020.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO framework. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review. Studies were excluded if they had been included in one of the SRMAs and if their key outcomes were already included in the reported meta-analysis.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE Profiles.

4. Summary of included studies

Eight papers were identified for inclusion (Bermudez et al 2020, Drane et al 2015, Gross et al 2018, Landazuri et al 2020, Sanjeet et al 2019, Wang et al 2020, Widjaja et al 2019, Xue et al 2018). Three were systematic review and meta-analyses (SRMAs) (Sanjeet et al 2019, Wang et al 2020, Xue et al 2018) which included between 189 and 414 patients who had MRgLITT from between nine and sixteen case series. One was a study including 58 subjects comparing cohorts undergoing stereotactic laser amygdalohippocampotomy (SLAH) or open resection (Drane et al 2015). Two included papers were retrospective case series; Bermudez et al 2020 included 26 patients and Gross et al 2018 included 58 patients. Landazuri et al 2020 was a case series which included prospectively collected data on 42 patients. Widjaja et al 2019 was a cost-utility study of MRgLITT and epilepsy surgery in adults with temporal lobe epilepsy. Table 1 provides a summary of these included studies and full details are given in Appendix E.

Table 1 Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Bermudez et al 2020 Retrospective case series Miami, USA	n= 26 Medically refractory focal epilepsy of mesial temporal origin. Mean (+/- SD) age: 42.3 years +/- 12.1 years.	**Intervention** MRgLITT performed by a single surgeon **Comparison** No comparator	**Critical Outcomes** • Free from disabling seizures (not defined) at mean 8.3 to 8.5 months f/u (reported by whether MRgLITT was on dominant or non-dominant hemisphere) • Neuropsychological outcomes at mean 8.4 months f/u **Important outcomes** • None reported
Drane et al 2015 Comparator cohort study Georgia, USA	n= 19 SLAH n= 39 open resection Medically refractory mesial temporal lobe epilepsy Age ≥18 years Mean age across groups 36-38.2 years	**Intervention** SLAH **Comparison** Open resection	**Critical Outcomes** • Seizure freedom (Engel class) at 6 months f/u • Neuropsychological outcomes (naming and recognition) at 6 months or 1 year f/u • Outcomes reported by whether dominant or non-dominant hemisphere intervention **Important outcomes** • None reported
Gross et al 2018 Retrospective case series Georgia, USA	n= 58 Focal epilepsy with unilateral anterior temporal onsets on scalp EEG and/or medial temporal onsets on invasive EEG.	**Intervention** SLAH **Comparison** No comparator	**Critical Outcomes** • Seizure freedom (Engel class) at 12 months f/u after first procedure and after latest procedure (reported for whole group and by whether MTS/ non-MTS)

	43 had mesial temporal sclerosis (MTS) demonstrated on MRI. Mean (+/- SD) age 40 years +/- 15 years. Age range 16 to 67 years.		• Neuropsychological outcomes (verbal learning) at average 6.4 months f/u **Important outcomes** • Complications at 12 months f/u
Landazuri et al 2020 Prospective case series 10 centres, USA	n= 42 Patients enrolled in the Laser Ablation of Abnormal Neurological Tissue Using Robotic NeuroBlate System (LAANTERN) registry who underwent MRgLITT for DRE. Mean (+/- SD) age: 35.1 years +/- 17.7 years. Mesial temporal lobe epilepsy (MTLE) / mesial temporal sclerosis epilepsy (MSE): 34 (56.7%)	**Intervention** MRgLITT **Comparison** No comparator	**Critical Outcomes** • Seizure freedom (Engel class) at 12 months f/u (reported for whole group and by whether MTLE/MSE or non-MTLE/MSE) • Quality of life (QOLIE-31) at latest f/u (duration not stated) **Important outcomes** • Hospitalisations • Procedure-related adverse events
Sanjeet et al 2019 SRMA of nine case series USA All included studies carried out in the USA	n=239 Subjects with temporal lobe-based seizure pathologic conditions. 78.6% had a lesional pathologic condition identified on MRI; the remainder had a nonlesional pathologic condition. Mean (+/- SD) age 40.9 years +/- 14 years	**Intervention** MRgLITT **Comparison** No comparator	**Critical Outcomes** • Seizure freedom (Engel class IA +/- IB) at 12 to 36 months f/u **Important outcomes** • Complication rate at median 22.4 months f/u • Reoperations at median 22.4 months f/u
Wang et al, 2020 SRMA of sixteen case series Beijing, China. All included studies carried out in the USA.	n=414 DRE Aetiologies included temporal lobe epilepsy, hypothalamic hamartoma, focal cortical dysplasia, tuberous sclerosis complex and periventricular nodular heterotopias. Age range 0.4 to 74 years.	**Intervention** MRgLITT **Comparison** No comparator	**Critical Outcomes** • Seizure freedom (Engel class I) for whole group and by aetiology of epilepsy (f/u period not stated, all >6 months) **Important outcomes** • Post-operative side-effects
Widjaja et al 2019 Cost-utility analysis Canada	Adults with drug resistant temporal lobe epilepsy who have undergone the same pre-surgical diagnostic evaluation and were deemed eligible for MRgLITT or epilepsy surgery. Hypothetical cohort.	**Intervention** MRgLITT **Comparison** Epilepsy surgery	**Critical Outcomes** • None reported **Important outcomes** • None reported **Cost-utility outcomes** • Costs

	Average age 35.8 years (SD 1.2 years).		• QALYs • Incremental cost-effectiveness ratio
Xue et al 2018 SRMA of twelve case series Tianjin, China. Included studies were carried out in the USA or Canada.	n= 189 Patients with epilepsy who were medication-resistant with focal onset of seizures. Underlying conditions were mesial temporal lobe epilepsy, temporal lobe epilepsy, lesional and localised epilepsy and insular epilepsy. Age range 1 to 69 years.	**Intervention** MRgLITT **Comparison** No comparator	**Critical Outcomes** • Seizure outcome (Engel class) at 7 days to 51 months f/u **Important outcomes** • Post-operative complications
Abbreviations: DRE: drug-resistant epilepsy; EEG: electroencephalogram; f/u: follow-up; LAANTERN: Laser Ablation of Abnormal Neurological Tissue Using Robotic NeuroBlate System; MRgLITT: MR-guided laser interstitial thermal therapy; MRI: magnetic resonance imaging; MSE: mesial temporal sclerosis epilepsy; MTLE: mesial temporal lobe epilepsy; MTS: mesial temporal sclerosis; QALY: Quality-adjusted life year; SD: standard deviation; SLAH: stereotactic laser amygdalohippocampotomy; SRMA: systematic review and meta-analysis;			

5. Results

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. In total, 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 [5]. **(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 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

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

	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.
	
	In total 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.
	  ○ 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.
	  ○ 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 ($p<0.01$).
	  ○ 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. 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:** Not applicable	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. **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. 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. **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. In total 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 **Certainty of evidence:** Very low	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 patients as the risks of reoperation can adversely impact their quality of life and function. 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.
[1] 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; [2] The QOLIE-31 includes 39 items in 6 sections: energy, emotional wellbeing, activities/ social, cognitive function, seizure worry, effects of medication; as well as two items about overall QOL and overall health. **Abbreviations:** CI: Confidence interval; Dom: language dominant hemisphere; DRE: drug-resistant 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 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	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	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	

6. Discussion

This review considered the evidence for the clinical effectiveness and safety of MR-guided Laser Interstitial Thermal Therapy (MRgLITT) compared to open neurosurgery or continued medical therapy alone for children and adults with refractory focal epilepsy when open neurosurgery carries a high risk of serious adverse effects. The critical outcomes of interest were seizure freedom, neuropsychological outcomes and quality of life. The important outcomes were need for medical therapy, hospitalisations and cognitive development in children. Evidence was also sought on safety, re-operation rate and cost effectiveness.

Evidence was available from three SRMAs with between 189 and 414 subjects from between nine and sixteen case series (Sanjeet et al 2019, Wang et al 2020, Xue et al 2018), one cohort study of 58 adults comparing those who had stereotactic laser amygdalohippocampotomy (SLAH) with those who had open resection (Drane et al 2015), three case series with between 26 and 58 subjects (Bermudez et al 2020, Gross et al 2018, Landazuri et al 2020), and one cost-utility study of MRgLITT or surgery (Widjaja et al 2019). All studies were at high risk of bias and certainty about the evidence for all critical and important outcomes was very low when assessed using modified GRADE.

All the interventions reported in all seven clinical effectiveness and safety studies were carried out in the USA or Canada. There was variation across the seven studies for the age of the subjects included as well as for aetiology of the focal epilepsy. Two SRMAs (Wang et al 2020, Xue et al 2018) and one case series (Gross et al 2018) included both adults and children, the comparator cohort study (Drane et al 2015) and the cost-utility study (Widjaja et al 2019) included adults only, and the three other studies did not state whether or not children were included but the mean (+/-SD) ages of their included subjects suggest that few or no children were included. Five studies included only subjects with focal epilepsy of temporal lobe origin (Bermudez et al 2020, Drane et al 2015, Gross et al 2018, Sanjeet et al 2019, Widjaja et al 2019). Three studies reported outcomes for groups of patients with epilepsy with a mix of aetiologies (Landazuri et al 2020, Wang et al 2020, Xue et al 2018) and two of these (Landazuri et al 2020, Wang et al 2020) also reported outcomes separately for subgroups of patients with other specific aetiologies.

Six of the seven clinical effectiveness studies reported seizure outcomes using the Engel classification (Wieser et al 2001). Seizure freedom was most often defined as Engel class I, which includes patients who are completely seizure free as well as those with non-disabling simple partial seizures, no disabling seizures for two years, and who have generalized convulsions with antiepileptic drug withdrawal only. One study reported only Engel class IA +/- IB (Sanjeet et al 2019) which includes those who are completely seizure-free or have non-disabling simple partial seizures. The seventh study (Bermudez et al 2020) reported patients who were free of disabling seizures, but this was not defined, and the cost-utility study (Widjaja et al 2019) did not state what seizure outcomes definition was used in their model.

Fewer studies reported results for the other outcomes relevant to this review. The comparator study and two case series reported neuropsychological outcomes, one case series reported quality of life, five studies reported procedural complications, one reported hospitalisation and one reported re-operations. Duration of follow-up was not clearly stated for all outcomes but ranged from six months (Drane et al 2015) to a maximum of 51 months (Xue et al 2018).

All studies reported improved seizure outcomes after MRgLITT, with the mean seizure free rate (Engel class I) ranging from 20% to 71% depending on the aetiology and duration of

follow-up. One study compared MRgLITT with open neurosurgical resection (Drane et al 2015) but the small numbers and lack of statistical measures mean that no conclusions can be drawn about the seizure outcomes compared with the minimum clinically important difference (MCID) threshold defined in the PICO.

One comparative study reported significantly worse naming and recognition outcomes at follow-up in some subjects undergoing open resection compared with those undergoing SLAH (Drane et al 2015) and reported that significantly more subjects undergoing open resection experienced a decline in these outcomes than those undergoing SLAH. Outcomes were reported at six months in the SLAH group and at one year in the open resection group; it is unclear whether this difference in follow-up had any effect on the outcomes reported. One case series reported significant improvement in one learning outcome and no significant differences in other learning and recall outcomes at follow-up after MRgLITT (Gross et al 2018).

The case series by Landazuri et al 2020 reported statistically significant improvements in two out of five quality of life subscores (seizure worry and social functioning) after MRgLITT, with no significant change in the overall quality of life score. The clinical significance of these changes in scores was not clear.

Five studies reported overall procedural complication rates of between 7% and 24% at between more than six months and a median 22.4 months follow-up after MRgLITT. Sanjeet et al 2019 reported that around 15% of patients required re-operation (including repeat LITT or anterior temporal lobectomy) up to a median of 22.4 months (range seven to 70 months) after MRgLITT.

The cost-utility study reported that surgery was more cost-effective than MRgLITT for adults with temporal lobe epilepsy, and surgery remained the preferred option in the majority of sensitivity analyses (Widjaja et al 2019). However there were several problems with this study which mean that the findings should be interpreted with caution. The populations undergoing surgery or MRgLITT were drawn from different studies and it was unclear how comparable they were. The authors found limited outcomes data for MRgLITT and some outcomes (for example neurological complications) were assumed to be the same as for surgery as there were no data. Canadian costs were used and the analyses were done from the Canadian healthcare payer perspective; it is unclear how generalisable this is to the NHS setting. Model inputs were taken from studies published between 1994 and 2019; the time period for costs used was not stated.

All the studies included observational evidence only. Drane et al 2015 compared outcomes for patients undergoing SLAH on their language dominant or non-dominant hemisphere but no other studies compared outcomes in groups of patients with different types of lesions or in different age groups. A number of other factors may have affected the outcomes and increased the uncertainty of the results. These include:

- All studies provided limited demographic or clinical information about the subjects.
- It is not clear to what extent this evidence applies to children. Two SRMAs (Wang et al 2020, Xue et al 2018) and one case series (Gross et al 2018) included both adults and children, and Drane et al 2015 and Widjaja et al 2019 included adults only. The remaining SRMA (Sanjeet et al 2019) and two case series did not report whether or not children were included.
- Two case series, and at least some of the studies included in two of the SRMAs, were retrospective. This adds potential biases due to risk of selection bias and incomplete reporting of the original cohort which may be harder to identify retrospectively. The

exceptions were the prospective cohort study by Drane et al 2015, the study by Landazuri et al 2020 which analysed prospectively collected data, and Xue et al 2018 who reported that their SRMA only included studies which collected data prospectively.

- All three case series reported some loss to follow-up.
- All three SRMAs assessed the risk of bias of their included studies using standard approaches. Two (Sanjeet et al 2019, Wang et al 2020) considered that their included studies had a high risk of bias. Xue et al 2018 included only studies which scored above a defined threshold on the MINORS (methodological index for nonrandomised studies) scale, reducing the risk of bias.
- There is some duplication of findings from the SRMAs as three studies were included in all three SRMAs and six studies were included in two of the SRMAs. Gross et al 2018 was included in the SRMAs by Sanjeet et al 2019 and Wang et al 2020, but was included separately in this review because the neuropsychological outcomes (a critical outcome) they reported were not included in the SRMAs.

7. Conclusion

This review included three SRMAs including between nine and sixteen case series, one comparator cohort study, and three case series two of which were retrospective and one prospective. These provide very low certainty evidence on critical and important outcomes following MRgLITT for children and adults with refractory focal epilepsy when open neurosurgery carries a high risk of serious adverse effects. All studies reported improvements in seizure outcomes which were reported at follow-up periods of from seven days to a maximum of 51 months, for groups of patients with drug-resistant focal epilepsy due to a variety of aetiologies. Improvements were also reported for patients with focal epilepsy arising from the temporal lobe and with other specific aetiologies including focal cortical dysplasia, tuberous sclerosis complex and periventricular nodular heterotopias. The comparator cohort study compared MRgLITT with open neurosurgical resection but the small numbers and lack of statistical measures mean that no conclusions can be drawn about the seizure outcomes reported compared with the MCID threshold defined in the PICO.

The comparator study and two case series also reported neuropsychological outcomes. Significantly worse naming and recognition outcomes were reported in some subjects undergoing open resection compared with those undergoing SLAH. One case series reported a significant improvement in one learning outcome and no significant differences in other learning and recall outcomes at follow-up after MRgLITT. One study reported a significant improvement in two quality of life subscores after MRgLITT with no change in the overall quality of life score. Five studies reported a range of complications following the procedure and one SRMA reported a re-operation rate of 15%. One cost-utility study reported that surgery was more cost-effective than MRgLITT.

The evidence from these studies must be regarded as very low certainty due to their design, conduct and reporting. There is a significant risk of bias associated with the case series design of three of the studies and with two of the SRMAs; the third SRMA excluded studies they judged to be at high risk of bias but still has some potential sources of bias. Limited details were provided about the study subjects included in all studies, and all three case series reported loss to follow-up. Methodological limitations of the cost-utility analysis mean that its findings should be interpreted with caution.

There was no evidence that there were any subgroups who may benefit from MRgLITT more than the general population of interest.

The studies identified for this review therefore provide very low certainty evidence that MRgLITT improves outcomes at follow-up for children and adults with refractory focal epilepsy in whom open neurosurgery carries a high risk of serious adverse effects. They also provide very low certainty evidence that neuropsychological outcomes are significantly worse in those undergoing open neurosurgery compared with MRgLITT, but no evidence on whether there is any significant difference in seizure outcomes after MRgLITT or open neurosurgery. It is not possible to draw conclusions about the outcomes of MRgLITT compared with continued medical therapy.

Appendix A PICO Document

The review questions for this evidence review are:

1. In adults and children with drug-resistant focal epilepsy who have identifiable epileptogenic zones, what is the clinical effectiveness of MR-guided LITT compared with open neurosurgical resection or continued medical therapy alone?

2. In adults and children with drug-resistant focal epilepsy with identifiable epileptogenic zones, what is the safety of MR-guided LITT compared with open neurosurgical resection or continued medical therapy alone?

3. In adults and children with drug-resistant focal epilepsy with identifiable epileptogenic zones, what is the cost-effectiveness of MR-guided LITT compared with open neurosurgical resection or continued medical therapy alone?

4. From the evidence selected, are there any subgroups of patients that may benefit from MR-guided LITT more than the wider population of interest?

P –Population and Indication	Adults and children with drug-resistant focal epilepsy[6] with identifiable epileptogenic lesions/zones[7] for which open neurosurgery is a viable option although would have clearly recognised serious side effects in these patients. Sub-groups of interest • Adults • Children above the age of 1 year • Lesion/zone type *[The side effects of open neurosurgery include impairment of motor function, vision, language and memory; MRgLITT would be an alternative with reduced risk of morbidity.]*
I – Intervention	• Magnetic resonance-guided laser interstitial thermal therapy (MRgLITT) [Systems for delivery of MRgLITT include Visualase and Neuroblate] *[Please note that MRI-guided laser interstitial thermal therapy (MRgLITT) may also be referred to as 'laser interstitial thermal therapy (LITT) in the literature. This is a minimally invasive treatment which can be used in focal refractory epilepsy. Continuous real-time MRI scanning is done to allow visualisation of the exact target area and a fine fibreoptic laser catheter is inserted into the target area under stereotactic guidance. Under computer guidance, laser energy is applied to the target area.]*
C – Comparator(s)	The alternative treatments to compare with MRgLITT are: • Open neurosurgical resection *[this could be described in the literature as surgical resection]* • Continued medical therapy alone *[The current standard treatment for the management of these groups of patients with drug-resistant focal epilepsy is open neurosurgery. Patients in whom surgery is contraindicated continue with medical management alone.]*
O – Outcomes .	**<u>Clinical Effectiveness</u>** Unless stated for the outcome, the minimum clinically important difference (MCID) is unknown. *<u>Critical to decision-making:</u>*

[6] Drug-resistant or refractory epilepsy is defined as failure to achieve adequate seizure control with adequate trials of two or more AEDs, taken individually or in combination.
[7] Epileptogenic lesions/zones including heterotopic nodules, focal cortical dysplasia, hippocampal sclerosis, as well as other lesions, low grade glioneuronal tumours, scar tissue and malformations occurring elsewhere in the brain

	• Seizure freedom *The minimum clinically important difference for this outcome can be considered as seizure freedom one-year post MRgLITT to be 10% better than conventional surgery. This can include the patient still experiencing auras, but with no seizures. The ILAE epilepsy surgery outcome scale can be used to quantify seizures post intervention. The Engel Epilepsy Surgery Outcome Scale is also used.* *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 overtime and improved quality of life.* • Neuropsychological outcomes *These include the effect on language, memory and executive function. This can be evaluated through a number of tools as reported in studies, including but not limited to the following:* o *Language can be evaluated using the Mckenna graded naming test, semantic fluency test and phonemic fluency test. Patients can have their visual and verbal memory tested through immediate and delayed recall of a complex figure and a short story.* o *The Wechsler Adult Intelligence Scale (WAIS) is an IQ test designed to measure intelligence and cognitive ability in adults and older adolescents. It has four components; verbal comprehension index, perceptual reasoning index, working memory index and processing speed index.* *This outcome is key to patients and their carers because it can help to identify areas of difficulty and improvement in cognitive function and the relationship between epilepsy and a patient's emotional function.* • Quality of life *To evaluate quality of life, the Quality of Life Epilepsy Inventory (QOLIE-89) contains comprehensive measures to evaluate overall quality of life, emotional well-being, social support, energy and fatigue, anxiety related to health, medication effects, health discouragement, work/driving/social function, attention/concentration, language, memory, physical function, pain, role limitations due to physical problems, and health perceptions. The shorter QOLIE-31 can also be used.* *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.* *Important to decision-making:* • Need for medical therapy *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.* *[Medication use should be assessed up to 1-year post-intervention.]* • Hospitalisations *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. • Cognitive development in children *This will be assessed through a number of assessments and tools as documented in the literature.* *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.* **Safety and adverse events** • Complications from procedure *Complications may include a persistent physical deficit including loss of limb power, loss of part of a field of vision, impairment of language or memory and endocrine complications.* *The minimum clinically important difference here is defined as a 10% reduction in complications and adverse events from procedures occurring using MRgLITT compared to conventional surgery.* *Procedural complications are important to patients because they are irreversible, can be serious and need be considered to inform treatment choices.* • 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 patients as the risks of reoperation can adversely impact their quality of life and function.* **Cost effectiveness**
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher-level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2010-2020
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-publication prints and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase and the Cochrane Library were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-publication prints and guidelines, case reports and resource utilisation studies were excluded.

Search dates: 1 January 2010 to 19th November 2020

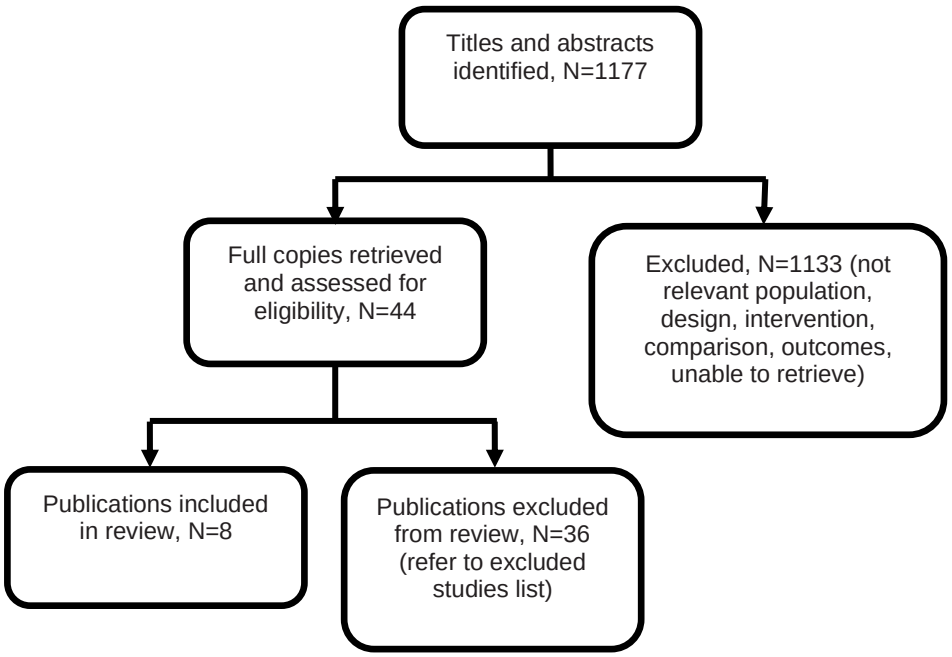
Medline search

# ▲	Searches
1	exp epilepsy/
2	epilep*.mp.
3	seizure*.mp.
4	1 or 2 or 3
5	laser.mp.
6	mrgLITT.mp.
7	LITT.mp.
8	exp laser therapy/ visualase.mp.
9	
10	neuroblate.mp.
11	5 or 6 or 7 or 8 or 9 or 10
12	hippocampal sclerosis.mp. or exp hippocampal sclerosis/
13	exp periventricular heterotopia/ or heterotopic nodules.mp. or periventricular heterotopia.mp.
14	exp cortical dysplasia/ or cortical dysplasia.mp.
15	low grade glioneuronal tumor.mp. or exp glioma/
16	scar tissue.mp. or exp scar tissue/
17	lesion.mp. or exp brain damage/
18	(epileptogenic or epileptogenesis or epileptic focus).mp.
19	12 or 13 or 14 or 15 or 16 or 17 or 18
20	4 and 11 and 19
21	limit 20 to (english language and yr="2010-Current")

Appendix C Evidence selection

The literature searches identified 1177 references. These were screened using their titles and abstracts and 44 references were obtained in full text and assessed for relevance. Of these, six references are included in the evidence summary. The remaining 36 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection decision and rationale if excluded
Rolston, J. and Chang, E., 2016. Stereotactic Laser Ablation for Hypothalamic Hamartoma. *Neurosurgery Clinics of North America*, 27(1), pp.59-67.	Excluded. Narrative review relating to HH.
Du, V., Gandhi, S., Rekate, H. and Mehta, A., 2017. Laser interstitial thermal therapy: A first line treatment for seizures due to hypothalamic hamartoma? *Epilepsia*, 58, pp.77-84.	Excluded. Eight patients with HH.
Xu, D., Chen, T., Hlubek, R., Bristol, R., Smith, K., Ponce, F., Kerrigan, J. and Nakaji, P., 2018. Magnetic Resonance Imaging-Guided Laser Interstitial Thermal Therapy for the Treatment of Hypothalamic Hamartomas: A Retrospective Review. *Neurosurgery*, 83(6), pp.1183-1192.	Excluded. Review of HH treatment.

Appendix D Excluded studies table

Study reference	Reason for exclusion
Cajigas I, Kanner AM, Ribot R, et al. Magnetic resonance-guided laser interstitial thermal therapy for mesial temporal epilepsy: a case series analysis of outcomes and complications at 2-year follow-up. World Neurosurg. 2019;126: e1121-e1129	No additional useful outcomes to those reported in SRs. Included in Wang et al SR.
Curry DJ, Gowda A, McNichols RJ, Wilfong AA. MR-guided stereotactic laser ablation of epileptogenic foci in children. Epilepsy and Behavior. 2012;24(4):408-14. http://dx.doi.org/10.1016/j.yebeh.2012.04.135	Small sample size, no additional useful outcomes to those reported in SRs. Included in Xue et al SR.
Donos C, Rollo P, Tombridge K, Johnson JA, Tandon N. Visual field deficits following laser ablation of the hippocampus. Neurology. 2020;94(12):e1303-e13. 10.1212/wnl.0000000000008940	Only outcome visual field deficit - included in other SRs/studies of complications.
Fayed I, Sacino MF, Gaillard WD, Keating RF, Oluigbo CO. MR-Guided Laser Interstitial Thermal Therapy for Medically Refractory Lesional Epilepsy in Pediatric Patients: Experience and Outcomes. Pediatric Neurosurgery. 2018;53(5):322-9. http://dx.doi.org/10.1159/000491823	Small sample size, no additional useful outcomes to those reported in SRs. 4 patients had HH. Included in Wang et al SR.
Grewal SS, Zimmerman RS, Worrell G, Brinkmann BH, Tatum WO, Crepeau AZ, et al. Laser ablation for mesial temporal epilepsy: A multi-site, single institutional series. J Neurosurg. 2019;1306(6):2055-62. http://dx.doi.org/10.3171/2018.2.JNS171873	No additional useful outcomes to those reported in SRs. Included in Sanjeet et al, Wang et al and Xue et al SRs.
Gupta K, Cabaniss B, Kheder A, Gedela S, Koch P, Hewitt KC, et al. Stereotactic MRI-guided laser interstitial thermal therapy for extratemporal lobe epilepsy. Epilepsia. 2020. 10.1111/epi.16614	No additional useful outcomes to those reported in SRs.
Hale AT, Sen S, Haider AS, Perkins FF, Clarke DF, Lee MR, et al. Open Resection versus Laser Interstitial Thermal Therapy for the Treatment of Pediatric Insular Epilepsy. Clinical Neurosurgery. 2019;85(4):E730-E6. http://dx.doi.org/10.1093/neuros/nyz094	LITT does not appear to have been MR-guided. No additional useful outcomes to those reported in SRs.
Hawasli AH, Bagade S, Shimony JS, Miller-Thomas M, Leuthardt EC. Magnetic resonance imaging-guided focused laser interstitial thermal therapy for intracranial lesions: Single-institution series. Neurosurgery. 2013;73(6):1007-17. http://dx.doi.org/10.1227/NEU.0000000000000144	Only one patient had epilepsy.
Jermakowicz WJ, Kanner AM, Sur S, Bermudez C, D'Haese PF, Kolcun JPG1, et al. Laser thermal ablation for mesiotemporal epilepsy: Analysis of ablation volumes and trajectories. Epilepsia. 2017;58(5):801-10. 10.1111/epi.13715	Outcomes not clearly reported allowing data extraction. Included in Sanjeet et al and Xue et al SRs.
Jermakowicz WJ, Wu C, Neal E, Cajigas I, D'Haese PF, Donahue DJ, et al. Clinically Significant Visual Deficits after Laser Interstitial Thermal Therapy for Mesiotemporal Epilepsy. Stereotactic & Functional Neurosurgery. 2019;97(5-6):347-55. https://dx.doi.org/10.1159/000504856	Survey of several institutions' results, with small sample size.
Kamath AA, Friedman DD, Hacker CD, Smyth MD, Limbrick DD, Jr., Kim AH, et al. MRI-Guided Interstitial Laser Ablation for Intracranial Lesions: A Large Single-Institution Experience of 133 Cases. Stereotactic & Functional Neurosurgery. 2017;95(6):417-28.	Only 11/120 patients had epilepsy foci. No additional useful PICO outcomes reported for this group.
Kang JY, Wu C, Tracy J, Lorenzo , Evans J, Nei M, et al. Laser interstitial thermal therapy for medically intractable mesial temporal lobe epilepsy. Epilepsia. 2015;57(2):325-34. 10.1111/epi.13284	No additional useful outcomes to those reported in SRs. Included in Sanjeet et al, Wang et al and Xue et al SRs.
Kerezoudis P, Parisi V, Marsh WR, Kaufman TJ, Lehman VT, Worrell GA, et al. Surgical Outcomes of Laser Interstitial Thermal Therapy for Temporal Lobe Epilepsy: Systematic Review and Meta-analysis. World Neurosurg. 2020;143:527-36.e3. http://dx.doi.org/10.1016/j.wneu.2020.07.194	Only 3 studies used MRI guidance in some but not all patients, remainder did not use MRI. Outcomes not reported separately for the MRI guidance studies.
King-Stephens D. What Is the Best Target for Ablation of Mesial Temporal Lobe Epilepsy? Epilepsy Currents. 2019;19(5):313-5. http://dx.doi.org/10.1177/1535759719868460	Commentary, not a report of study results or SR.

Le S, Ho AL, Fisher RS, Miller KJ, Henderson JM, Grant GA, et al. Laser interstitial thermal therapy (LITT): Seizure outcomes for refractory mesial temporal lobe epilepsy. Epilepsy and Behavior. 2018;89:37-41. http://dx.doi.org/10.1016/j.yebeh.2018.09.040	No additional useful outcomes to those reported in SRs. Included in Wang et al SR.
Lewis EC, Weil AG, Duchowny M, Bhatia S, Ragheb J, Miller I. MR-guided laser interstitial thermal therapy for pediatric drug-resistant lesional epilepsy. Epilepsia. 2015;56(10):1590-8. 10.1111/epi.13106	No additional useful outcomes to those reported in SRs. Included in Wang et al and Xue et al SRs.
McCracken DJ, Willie JT, Fernald BA, Saindane AM, Drane DL, Barrow DL, et al. Magnetic resonance thermometry-guided stereotactic laser ablation of cavernous malformations in drug-resistant epilepsy: Imaging and clinical results. Oper Neurosurg (Hagerstown). 2016;12(4):39-48. http://dx.doi.org/10.1227/NEU.0000000000001033	Small sample size, no pooled outcomes.
Perry MS, Donahue DJ, Malik SI, Keator CG, Hernandez A, Reddy RK, et al. Magnetic resonance imaging-guided laser interstitial thermal therapy as treatment for intractable insular epilepsy in children. J Neurosurg Pediatr. 2017;20(6):575-82. 10.3171/2017.6.Peds17158	No additional useful outcomes to those reported in SRs. Included in Xue et al SR.
Petito GT, Wharen RE, Feyissa AM, Grewal SS, Lucas JA, Tatum WO. The impact of stereotactic laser ablation at a typical epilepsy center. Epilepsy & Behavior. 2018;78:37-44. https://dx.doi.org/10.1016/j.yebeh.2017.10.041	No additional useful outcomes to those reported in SRs. Included in Wang et al SR.
Rennert RC, Khan U, Bartek J, Tatter SB, Field M, Toyota B, et al. Laser ablation of abnormal neurological tissue using robotic neuroblate system (laantern): Procedural safety and hospitalization. Neurosurgery. 2020;86(4):538-47. http://dx.doi.org/10.1093/neuros/nyz141	16/100 patients had epilepsy, not reported separately from rest of cohort.
Sacino M, Huang SS, Alexander H, Fayed I, Keating RF, Oluigbo CO. An Initial Cost-Effectiveness Analysis of Magnetic Resonance-Guided Laser Interstitial Thermal Therapy in Pediatric Epilepsy Surgery. Pediatr Neurosurg. 2020;55(3):141-8. 10.1159/000509329	Cost study, 25% of patients had HH.
Satzer D, Tao JX, Issa NP, Chen Z, Wu S, Rose S, et al. Stereotactic laser interstitial thermal therapy for epilepsy associated with solitary and multiple cerebral cavernous malformations. Neurosurg. 2020;48(4):E12. https://dx.doi.org/10.3171/2020.1.FOCUS19866	Small sample size, no additional useful outcomes to those reported in SRs.
Sharma M, Ball T, Alhourani A, Ugiliweneza B, Wang D, Boakye M, et al. Inverse national trends of laser interstitial thermal therapy and open surgical procedures for refractory epilepsy: a Nationwide Inpatient Sample-based propensity score matching analysis. Neurosurg Focus. 2020;48(4):E11. 10.3171/2020.1.Focus19935	Study of national trends in LITT use (USA).
Tao JX, Wu S, Lacy M, Rose S, Issa NP, Yang CW, et al. Stereotactic EEG-guided laser interstitial thermal therapy for mesial temporal lobe epilepsy. J Neurol Neurosurg Psychiatry. 2018;89(5):542-8. 10.1136/jnnp-2017-316833	Subjects had invasive EEG monitoring to localise lesions in addition to MRI.
Tatum WO, Thottempudi N, Gupta V, Feyissa AM, Grewal SS, Wharen RE, et al. De novo temporal intermittent rhythmic delta activity after laser interstitial thermal therapy for mesial temporal lobe epilepsy predicts poor seizure outcome. Clinical Neurophysiology. 2019;130(1):122-7. http://dx.doi.org/10.1016/j.clinph.2018.11.012	LITT does not appear to have been MR-guided.
Tovar-Spinoza Z, Ziechmann R, Zyck S. Single and staged laser interstitial thermal therapy ablation for cortical tubers causing refractory epilepsy in pediatric patients. Neurosurg. 2018;45(3):E9. http://dx.doi.org/10.3171/2018.6.FOCUS18228	Small sample size.
Vakharia VN, Sparks R, Li K, O'Keeffe AG, Miserocchi A, McEvoy AW, et al. Automated trajectory planning for laser interstitial thermal therapy in mesial temporal lobe epilepsy. Epilepsia.2018;59:814-824	No additional useful outcomes to those reported in SRs. Included in Sanjeet et al and Xue et al SRs.
Wang S, Rotenberg A, Bolton J. Patterns of anti-seizure medication (ASM) use in pediatric patients with surgically managed epilepsy: A retrospective review of data from Boston Children's Hospital. Epilepsy Research. 2020;160 (no pagination).	No PICO outcomes reported.
Waseem H, Osborn K, Schoenberg M, Kelley V, Bozorg A, Cabello D, et al. Laser ablation therapy: an alternative treatment for medically resistant mesial temporal lobe epilepsy after age 50. Epilepsy & behavior [Internet]. 2015; 51:[152?7 pp.]. 10.1016/j.yebeh.2015.07.022	Small sample size, larger studies reporting neuropsychologcal outcomes available. Included in Wang et al SR.

Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01090476/full.	
Waseem H, Vivas AC, Vale FL. MRI-guided laser interstitial thermal therapy for treatment of medically refractory non-lesional mesial temporal lobe epilepsy: Outcomes, complications, and current limitations: A review. Journal of Clinical Neuroscience. 2017;38:1-7. http://dx.doi.org/10.1016/j.jocn.2016.12.002	Non-systematic review of 38 patients selected from other published papers. Included in Sanjeet et al SR.
Whiting AC, Bingaman JR, Catapano JS, Whiting BB, Godzik J, Walker CT, et al. Laser Interstitial Thermal Therapy for Epileptogenic Periventricular Nodular Heterotopia. World Neurosurg. 2020;138:e892-e7. http://dx.doi.org/10.1016/j.wneu.2020.03.133	Small sample size, no additional useful outcomes to those reported in SRs.
Willie JT, Laxpati NG, Drane DL, Gowda A, Appin C, Hao C, et al. Real-time magnetic resonance-guided stereotactic laser amygdalohippocampotomy for mesial temporal lobe epilepsy. Neurosurgery. 2014;74(6):569-84. http://dx.doi.org/10.1227/NEU.0000000000000343	Small sample size, no additional useful outcomes to those reported in SRs.
Willie JT, Malcolm JG, Stern MA, Lowder LO, Neill SG, Cabaniss BT, et al. Safety and effectiveness of stereotactic laser ablation for epileptogenic cerebral cavernous malformations. Epilepsia. 2019;60(2):220-32. 10.1111/epi.14634	No additional useful outcomes to those reported in SRs. Included in Wang et al SRMA.
Wu C, JermakowiczWJ, Chakravorti S, et al. Effects of surgical targeting in laser interstitial thermal therapy for mesial temporal lobe epilepsy: a multicenter study of 234 patients. Epilepsia. 2019;60(6):1171-1183	Data retrospectively collected from 11 centres. Smaller than the SRs, and no additional outcomes reported. No clinical/demographic information about the patients.
Youngerman BE, Oh JY, Anbarasan D, Billakota S, Casadei CH, Corrigan EK, et al. Laser ablation is effective for temporal lobe epilepsy with and without mesial temporal sclerosis if hippocampal seizure onsets are localized by stereoelectroencephalography. Epilepsia. 2018;59(3):595-606. 10.1111/epi.14004	No before-after comparison, comparisons are between different methods used to localise lesions. Included in Sanjeet et al, Wang et al and Xue et al SRs.
Youngerman BE, Save AV, McKhann GM. Magnetic Resonance Imaging-Guided Laser Interstitial Thermal Therapy for Epilepsy: Systematic Review of Technique, Indications, and Outcomes. Neurosurgery. 2020;86(4):E366-E82. 10.1093/neuros/nyz556	Narrative review, no pooling of study results.

Appendix E Evidence Table

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Bermudez CI, Jermakowicz WJ, Kolcun JPG, Sur S, Cajigas I, Millan C, et al. Cognitive outcomes following laser interstitial therapy for mesiotemporal epilepsies. Neurol Clin Pract. 2020;10(4):314-23. 10.1212/cpj.0000000000000728 **Study location** Miami, USA **Study type** Retrospective case series **Study aim** To provide a review of cognitive outcomes across a full neuropsychological profile in patients who underwent laser interstitial thermal therapy for mesiotemporal epilepsy (mTLE). **Study dates** 2013-2016	**Study inclusion criteria** Medically refractory focal epilepsy of mesial temporal origin. Underwent LITT. Consecutive patients. **Study exclusion criteria** None stated **Total sample size** n=26 **Baseline characteristics** Total sample: Male: 58% Mean age: 42.3 +/- 12.1 years White: 85%, Black: 15% Hispanic/Latino: 78%, non-Hispanic: 22% Mean years of education: 11.7 +/- 2.9 years. Mean age at onset of seizure disorder: 15.03 +/- 13.61 years (range 1.0 to 59.0 years). 14 subjects had radiographic evidence of mesial temporal sclerosis. Outcomes were analysed by whether subjects underwent LITT on their dominant (n=13) or non-dominant (n=13) hemisphere based on language lateralisation. There were no significant differences in baseline characteristics between these two groups.	**Intervention details** MRgLITT performed by a single surgeon **Comparator details** No comparator	**Critical outcomes** Dom: surgery on dominant hemisphere Non-dom: surgery on non-dominant hemisphere Mean follow-up 8.4 months (+/- 3.3 months) *Seizure freedom (free of disabling seizures)* Dom: 85% (11/13) Non-dom: 75% (10/13) (no CI reported) *Neuropsychological outcomes* Mean pre-op score (SD), mean follow-up score (SD) (no significance measures reported for any outcomes) Wechsler memory scale Dom (n=10): 43.6 (13.9); 41.7 (13.4) Non-dom (n=6): 45.3 (10.9); 48.8 (3.4) List learning (% learned) Dom (n=10): 57.0% (12.1); 57.2% (13.1) Non-dom (n=9): 58.7% (18.5); 66.9% (14.6) List learning retention (% retained) Dom (n=10): 47.3% (19.2); 39.8% (25.9)	This study was appraised using the JBI critical appraisal checklist for case series 1. Yes 2. Unclear 3. Yes 4. Yes 5. No 6. Yes 7. No 8. Yes 9. No 10. No **Other comments:** This was a retrospective case series of subjects with focal epilepsy of mesial temporal origin. It reports outcomes from procedures by a single surgeon and it is not clear how generalisable these would be to other settings. Limited clinical information was provided about study subjects. The reporting of outcomes measures included between 16 and 21 of the original 26 subjects included; it is not clear why others were not included and whether they differed from those included. The seizure outcome 'free of disabling seizures' was not further defined. The numbers included in the neuropsychological

			Non-dom (n=9): 62.0% (21.2); 73.2% (14.6) BVMT-R (visual memory) total T-score Dom (n=8): 35.7 (10.6); 38.3 (13.9) Non-dom (n=8): 31.8 (12.9); 35.9 (12.1) Naming (% correct) Dom (n=11): 63.3% (14.7); 60.5% (20.4) Non-dom (n=10): 68.9% (16.8); 72.2% (16.6) COWAT (verbal fluency) phonemic (eg. words beginning with a specified letter) T-score Dom (n=11): 41.1 (11.8); 44.9 (12.5) Non-dom (n=9): 42.4 (18.0); 50.3 (10.7) COWAT (verbal fluency) semantic (eg. types of objects) T-score Dom (n=11): 40.6 (11.8); 39.4 (9.9) Non-dom (n=9): 44.0 (9.8); 39.8 (9.5) Trails A (processing speed) T score Dom (n=9): 35.8 (10.9); 40.0 (10.3 Non-dom: (n=6): 32.8 (4.0); 46.2 (8.7) Grooved pegboard test (fine motor dexterity) Dom (n=11): 36.5 (8.8); 38.9 (8.7)	outcomes reported were small and there are no measures of statistical significance so it is not possible to interpret the differences in scores between pre-op and follow-up, and their clinical significance is not clear. **Source of funding:** No comment on source of funding.

			Non-dom (n=7): 36.0 (9.2); 41.7 (10.1) **Important outcomes** None reported	
Drane DL, Loring DW, Voets NL, Price M, Ojemann JG, Willie JT, et al. Better object recognition and naming outcome with MRI-guided stereotactic laser amygdalohippocampotomy for temporal lobe epilepsy. Epilepsia 2015, 56(1):101–113. doi: 10.1111/epi.12860 **Study location** Georgia, USA **Study type** Comparator cohort study **Study aim** To identify whether stereotactic laser amygdalohippocampotomy (SLAH) would minimize deficits in category-related object recognition and naming in patients with temporal lobe epilepsy compared with standard surgical approaches. **Study dates** Not stated.	**Study inclusion criteria** Medically intractable mesial temporal lobe epilepsy. ≥18 years of age **Study exclusion criteria** Age < 18 years. **Total sample size** n=39 open resection (22 dominant/ 17 non-dominant*) n=19 SLAH (10 dominant/ 9 non-dominant) **Baseline characteristics** All native English speakers. All were left-hemisphere dominant for language, with the exception of two SLAH patients. Baseline characteristics in open resection dominant, SLAH dominant, open resection non-dominant, SLAH non-dominant respectively were: Age (years) 36, 38.2, 36.5, 36.2 (ns**) Age of onset (years): 16.7, 12.4, 13.9, 15.4 (ns) Number of AEDs: 2.1, 2.5, 2.0, 1.6 (ns)	**Intervention details** MR-guided SLAH **Comparator details** Open resection: tailored (n = 18) or standard (n = 4) anterior temporal lobectomy followed by mesial temporal resection, or selective transcortical amygdalohippocampectomy (SAH) (n = 17), affecting several temporal lobe regions	**Critical outcomes** Dom= procedure on language dominant hemisphere Non-dom= procedure on non-dominant hemisphere *Seizure outcomes, Engel Class I to IV* No. with seizure outcome, 6-month f/u (No significance measures reported) Dom: SLAH; open resection Engel I: 7/10; 11/22 Engel II: 1/10; 5 /22 Engel III: 2/10; 3/22 Engel IV: 0/10; 3/22 Non-dom: SLAH; open resection Engel I: 4/9; 13/17 Engel II: 0/9; 2/17 Engel III: 2/9; 2/17 Engel IV: 3/9; 0/17 *Neuropsychological outcomes* [8] Mean score (SD) at baseline; mean change in score (SD) at 6-month f/u for SLAH patients and 1-year f/u for open resection patients (higher scores better)	This study was appraised using the JBI critical appraisal checklist for cohort studies 1. Unclear 2. Yes 3. Yes 4. Yes 5. Yes 6. No 7. Unclear 8. Yes 9. N/A 10. Yes **Other comments:** This was a cohort study of subjects with temporal lobe epilepsy which compared subjects by hemisphere of intervention and intervention type (open surgery or SLAH). Limited clinical and demographic information was provided about the participants and there were significant baseline differences between groups in education. The study was carried out at two centres; all subjects at the University of Washington underwent open resection, while subjects at

[8] Common object naming was tested using the Boston Naming Test (BNT) which includes primarily manmade objects. Famous face recognition and naming was assessed with the modified Iowa Famous Faces Test. If an object or famous face could not be named, recognition was established based on verbal description, with sufficient detail to demonstrate knowledge.

	Years of education: 12.1, 12.5, 15.7, 15.4 (significant differences between all groups) Number with mesial temporal sclerosis (MTS): 10/22, 9/17, 7/10, 3/9 (ns) *Dominant: procedure on language dominant hemisphere Non-dominant: procedure on non-dominant hemisphere **ns: no significant difference between groups		*Boston Naming Test** Dom SLAH: 70.3 (22.4); 8.6 (25.7) Dom open: 76.6 (14.5); -23.6** (17.6) Non-dom SLAH: 85.6 (11.1); 3.2 (3.7) Non-dom open: 92.7 (7.0); 1.9 (4.8) *Famous face naming** Dom SLAH: 67.0 (23.6); 9.4 (12.5) Dom open: 69.9 (21.2); -28.3** (30.5) Non-dom SLAH: 89.9 (6.0); 7.6 (12.6) Non-dom open: 89.7 (6.9); 1.4 (8.1) *Famous face recognition* Dom SLAH: 72.9 (16.7); 4.2 (5.5) Dom open: 66.1 (15.2); 0.5 (13.2) Non-dom SLAH: 74.0 (16.6); 5.0 (4.9) Non-dom open: 76.0 (18.8); -9.0*** (16.5) *significant differences between groups on both naming tests at baseline (both dom groups worse than non-dom groups), p<0.001 **significantly different from other 3 groups, p<0.01 ***significantly different from other 3 groups, p<0.001 *Number of patients declining on one or more naming or recognition tasks* SLAH: 0/19 Open resection: 32/39	Emory University underwent either open resection or SLAH. Here subjects recruited earlier all underwent open resection, while later subjects were given a choice of procedure and most chose SLAH. The authors reported that anyone eligible for open surgery was eligible for SLAH. One eligible SLAH patient was excluded because they did not undergo cognitive assessment. There were no details on the assessment process or whether assessments were blinded. Subjects having intervention on their dominant hemisphere had significantly worse baseline performance on naming tests than those having intervention on their non-dominant hemisphere. The MCID was defined in the PCIO as 'seizure freedom one-year post MRgLITT 10% better than conventional surgery'. 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

			p < 0.0001 **Important outcomes** None reported	measures were reported for seizure outcomes so a comparison with MCID is not possible. Neuropsychological outcomes were reported at 6 months for SLAH patients and 1 year for open resection patients. The authors stated in the text that they did not identify any correlations between demographic or disease related variables and the change scores, but adjusted analyses for MTS status and age of onset. No further details were provided. **Source of funding:** The study was partially supported by grants from the National Institutes of Health/National Institute of Neurological Disorders and Stroke. Funding was also provided to Emory University by way of a clinical study agreement from Visualase, Inc., which assisted with some of the study-related costs of the patients undergoing the SLAH procedure only.
Gross RE, Stern MA, Willie JT, Fasano RE, Saindane AM, Soares BP, et al. Stereotactic	**Study inclusion criteria** Underwent stereotactic laser amygdalohippocampotomy (SLAH)	**Intervention details** SLAH *	**Critical outcomes** *Seizure freedom (Engel class I)* [9]	This study was appraised using the JBI critical appraisal checklist for case series

[9] 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

Laser Amygdalohippocampotomy for Mesial Temporal Lobe Epilepsy. Annals of Neurology. 2018;83(3):575-87. 10.1002/ana.25180 **Study location** Georgia, USA **Study type** Retrospective case series **Study aim** To evaluate the outcomes one-year and longer following stereotactic laser amygdalohippocampotomy for mesial temporal lobe epilepsy in a large series of patients treated over a five-year period **Study dates** 2011-2016	for mesial temporal lobe epilepsy (MTLE) Electrographic evidence of unilateral anterior temporal onsets on scalp EEG and/or medial temporal onsets on invasive EEG, with concordant mesial temporal sclerosis (MTS), if present, and/or concordant temporal hypometabolism on PET **Study exclusion criteria** None stated **Total sample size** n=58 **Baseline characteristics** Female: 33 (56.9%) Age range 16 to 67 years Mean (+/- SD) age 40 years +/-15 years 43 had MTS demonstrated on MR imaging	49 had a single procedure, 9 patients had repeat procedures. 30 patients underwent right-sided and 28 left-sided procedures **Comparator details** No comparator. *Note- the description of SLAH provided is equivalent to MRgLITT	(n=58, 12-month f/u after the first procedure) All patients, n=58 48.3% (95% CI 35.9 to 50.8) MTS, n=43 58.1% (95% CI 43.3 to 71.6) Non-MTS, n=15 20.0% (95% CI 6.3 to 46.0) *Seizure outcomes, Engel Class I to IV* (n=58, 12-month f/u after the latest procedure) All patients, n=58 I: 31* (53.4% (95% CI 40.8 to 65.7)) II: 13 (22.4%) III: 11 (19.0% IV: 3 (5.2%) *Of whom 1A: 22; 1B: 7; 1D: 2. MTS, n=43 I: 26 (60.5% (95% CI 45.6 to 73.7)) II: 10 (23.2%) III: 7 (16.3%) IV: 0 Non-MTS, n=15 I: 5 (33.3% (95% CI 15.0 to 58.5)) II: 3 (20.0%) III: 4 (26.7%)	11. Yes 12. Yes 13. Yes 14. Yes 15. Yes 16. No 17. No 18. Yes 19. No 20. No **Other comments:** This was a retrospective case series of subjects with mesial temporal lobe epilepsy. Limited clinical and demographic information was provided about the participants. Detailed 12-month seizure outcomes were reported 12 months after the last procedure, whether this was the first or repeat procedure, therefore for 9 patients these outcomes were after two procedures and for 49 they were after one procedure. Verbal memory outcomes were only reported for 49/58 patients and it was not clear whether these were after the first or latest procedure and whether the excluded patients differed from those included. Significance measures were only reported for some outcomes.

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;

			IV: 3 (20.0%) *Seizure freedom at 24 months after the latest procedure* (Kaplan-Meier analysis) All patients, n=58 34.3% (95% CI 19.7 to 49.3) *Neuropsychological outcomes: verbal memory scores* *RAVLT (Rey auditory verbal learning test)* (higher score better) n=49, f/u average 6.4 (+/- 1.5) months (range 5-11 months) (not stated whether this was after the first or latest procedure) Mean score +/- SD (range), pre SLAH; post SLAH Dom: language dominant hemisphere SLAH Non-dom: non-dominant hemisphere SLAH *RAVLT-learning* All (n=49): 41.8 +/- 10.8 (14 to 65); 41.9 +/- 11.6 (11 to 59), ns Dom (n=20): 37.4 +/- 10.7 (14 to 62); 35.3 +/- 12.7 (11 to 56), ns Non-dom (n=29): 44.9 +/- 10.0 (33 to 65); 46.6 +/- 8.3 (22 to 59), ns *RAVLT-Delayed recall* All (n=49): 5.9 +/- 3.9 (0 to 15); 6.5 +/- 4.1 (0 to 14), ns Dom (n=20): 4.6 +/- 3.7 (0 to 13); 4.2 +/- 3.4 (1 to 12), ns Non-dom (n=29): 6.6 +/- 3.9 (1 to 15); 8.2 +/- 3.7 (0 to 14), p<0.05 ns: difference not significant	**Source of funding:** This project was in part supported by a research grant from Visualase Inc and grants received by one author from the National Institute of Neurological Disorders and Stroke of the National Institutes of Health.

			Important outcomes None reported **Safety** *Complications* Visual field deficit: 5/58 (8.6%), of which one (1.7%) was persistent and symptomatic.	
Landazuri P, Shih J, Leuthardt E, Ben-Haim S, Neimat J, Tovar-Spinoza Z, et al. A prospective multicenter study of laser ablation for drug resistant epilepsy - One year outcomes. Epilepsy Res. 2020;167 (no pagination). http://dx.doi.org/10.1016/j.eplepsyres.2020.106473 **Study location** USA (10 centres) **Study type** Prospective case series **Study aim** To report one-year seizure outcomes, procedural data, and quality of life scores following laser interstitial thermal therapy (LITT) of epileptogenic foci **Study dates** Not stated	**Study inclusion criteria** Patients enrolled in the Laser Ablation of Abnormal Neurological Tissue Using Robotic NeuroBlate System (LAANTERN)[10] registry who underwent MRgLITT for DRE. **Study exclusion criteria** None stated **Total sample size** n=42 **Baseline characteristics** Mean (SD) age: 35.1 (17.7) Female, no (%): 33 (55%) Race/ethnicity, no. (%): White 51 (85%) Black/African American 4 (6.7%) Other/Unknown 5 (8.3%) Epilepsy aetiology, no (%): Mesial temporal lobe epilepsy (MTLE) / mesial temporal sclerosis epilepsy (MSE): 34 (56.7%) Hypothalamic hamartoma: 2 (3.3%) Cortical heterotopia / dysplasia: 7 (11.7%) Cavernous hemangioma: 2 (3.3%) Tuberous sclerosis: 2 (3.3%)	**Intervention details** MRgLITT (Neuroblate) **Comparator details** No comparator	**Critical outcomes** 42 patients completed 12-month f/u 22 patients completed 24-month f/u *Seizure freedom* (n=42, 12-month f/u) *Engel Class I* Total cohort (n=42): 27/42, 64.3% (95% CI 48.0 to 78.5) MTLE/MSE (n=24): 17/24, 70.8 % (95% CI 48.9 to 87.4) Non-MTLE/MSE (n=18): 10/18, 55.6% (95% CI 30.8 to 78.5) MTLE/MSE vs non-MTLE/MSE: p=0.1642 *Engel Class II* Total cohort 4/42, 9.5% MTLE/MSE 3/24, 12.5% Non-MTLE/MSE 1/18, 5.6% (no CI reported) *Engel Class III* Total cohort 9/42, 21.4%	This study was appraised using the JBI critical appraisal checklist for case series 1. Yes 2. Unclear 3. Unclear 4. Unclear 5. No 6. Yes 7. No 8. Yes 9. No 10. No **Other comments:** This study reported prospectively collected data from a subgroup of patients included in LAANTERN, a multicentre study of LITT for patients with epilepsy. The included patients were those who had had LITT due to DRE, but it was not clear how their conditions were identified and whether all eligible patients were included, and there was limited clinical information about them. 57% of the total

[10] The LAANTERN registry is described as an ongoing multisite study designed to enrol up to 1000 patients undergoing LITT for epilepsy and prospectively collect clinical, outcomes, and imaging data. LAANTERN enrolment and five year follow-up is estimated to be complete in 2027.

	Seizure focus/SEEG target: 13 (21.7%) (note: these aetiologies relate to n=60 patients. Most outcomes include fewer patients)		MTLE/MSE 4/24, 16.7% Non-MTLE/MSE 5/18, 27.8% (no CI reported) *Engel Class IV* Total cohort 2/42, 4.8% (95% CI 0.6 to 16.2) MTLE/MSE 0 Non-MTLE/MSE 2/18, 11.1% (no CI reported) *Quality of Life (QOLIE-31 score)* [11] (n=29, reported at last f/u; duration of f/u not stated) Higher score better *Median total QOLIE-31 score* Baseline: 51.7 (range 8.7 to 77.3) Last f/u: 65.8 (range not stated) p=0.2173 *Median improvement in QOLIE-31 subscores* (actual scores not reported): Seizure worry: +15 (p = 0.0219) Emotional wellbeing: +8 (ns) Energy/ fatigue: +5 (ns) Cognitive function: +7 (ns) Social functioning: +15 (p = 0.0175) (ns: not significant) **Important outcomes** *Hospitalisations* (n included for this outcome not stated).	cohort of 60 and of the 42 for whom seizure outcomes were reported had epilepsy of temporal lobe origin and the remainder had other specific aetiologies. The aetiologies of those included in the QOLIE-31 analysis and the hospitalisations outcome were not described. Four subjects were reported to be lost to follow-up, although it is not clear at what stage they were lost and whether they were included in any of the outcomes reported. Significance measures were only reported for some of the outcomes. The duration of f/u for the QOLIE-31 was not reported and the clinical significance of the changes in QOLIE-31 scores reported is not clear. **Source of funding:** The LAANTERN registry is sponsored by Monteris Medical, Inc.

[11] The QOLIE-31 includes 39 items in 6 sections: energy, emotional wellbeing, activities/ social, cognitive function, seizure worry, effects of medication; as well as two items about overall QOL and overall health.

			One patient was rehospitalised within 90 days for increased seizures which improved after repeat LITT. **Safety** Procedure-related adverse events: 5/60 (8.3%) 'Not serious': 4 (eg headache, mild aphasia) 'Serious': 1 (defined as seizures, repeat surgery resulting in intraparenchymal haemorrhage requiring decompressive craniectomy and duraplasty, or neurological sequelae which were reported to resolve by 12 months).	
Sanjeet SG, Mohammed Ali A, Victor ML, Waseem W, Gregory AW, William T, et al. Magnetic Resonance-Guided Laser Interstitial Thermal Therapy Versus Stereotactic Radiosurgery for Medically Intractable Temporal Lobe Epilepsy: A Systematic Review and Meta-Analysis of Seizure Outcomes and Complications. World Neurosurg. 2019;122:e32-e47. 10.1016/j.wneu.2018.08.227 **Study location** USA All included studies carried out in the USA. **Study type** SRMA of observational studies. **Study aim**	**Study inclusion criteria** Subjects with temporal lobe-based seizure pathologic conditions. Explicitly describe the surgical technique as either MRgLITT or Stereotactic Radiosurgery (SRS) only without adjunct therapy. Minimum 12-month f/u. Published in English. **Study exclusion criteria** Cohorts involving pathologic conditions not related to epilepsy. Cohorts reporting outcomes other than Engel classification or complications. Case reports. Conference abstracts without full text. **Total sample size** n=250 in 9 MRgLITT studies **Baseline characteristics**	**Intervention details** MRgLITT **Comparator details** No comparator. The review also reported separately outcomes for subjects undergoing SRS in 10 studies but there were no comparative studies.	**Critical outcomes** Median f/u 22.4 months (range 7-70 months across studies) *Seizure freedom* * Overall seizure freedom at 12 to 36 months (n=250, 9 studies): Mean incidence 50%, (95% CI 44 to 56) I^2 =0.00, p=0.78 **Important outcomes** None reported **Safety** *Complications* (n=207, 8 studies) Overall complication rate 20% (95% CI 14 to 26) I^2 =0.00, p=0.63 Visual field deficits: n=12 Cranial nerve deficits: n=8 Headache, nausea, and gait abnormalities: n=9	This study was appraised using the JBI critical appraisal checklist for systematic reviews and research synthesis 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Yes 8. Yes 9. No 10. NA 11. Yes **Other comments:** This SRMA included observational studies only. Subjects had drug-resistant mesial temporal lobe epilepsy; 78.6% of all subjects had a lesion identified on MRI, the remainder had a nonlesional

To systematically review the current literature summarizing the effects of MRgLITT and SRS in the management of mesial temporal lobe epilepsy (MTLE) **Study dates** Search to May 2018. Included studies were published in 2016-2018.	Mean age, 40.9 years; SD +/- 14 years Male: 53.9% Left side involvement 51.6% (112/217) 78.6% (n = 188/239) patients had a lesional pathologic condition identified on MRI; the remainder had a nonlesional pathologic condition which was determined by other invasive electroencephalographic monitoring.		Cerebral haemorrhage: n=4 *Re-operations* ** (n=184, 7 studies) Mean re-operation rate: 15% (95% CI 9 to 22) I^2 =19.87, p=0.28 *Seizure freedom appears to be defined as Engel Class IA or Engel Class IA + IB ** Re-operations reported in individual studies included repeat LITT and anterior temporal lobectomy but there were no further details.	pathologic condition. There was limited information about patient clinical or demographic background. Authors assessed risk of bias using a standard approach and used a modified GRADE approach to assess certainty of evidence; based on this they concluded that their confidence in all effect estimates was very low. The outcome was reported as 'complete seizure freedom as described by the Engel scale at least one year of follow-up'. It appeared from results reported in one table that this included Engel class IA only where this was reported separately, and Engel class IA and IB where they were reported combined, but this was not explicitly stated. **Source of funding:** No comment on source of funding.
Wang Y, Xu J, Liu T, Chen F, Chen S, Xie Z, et al. Magnetic resonance-guided laser interstitial thermal therapy versus stereoelectroencephalography-guided radiofrequency thermocoagulation for drug-resistant epilepsy: A systematic review and meta-analysis. Epilepsy Res. 2020;166 (no pagination). http://dx.doi.org/10.1016/j.eplepsyres.2020.106397	**Study inclusion criteria** Prospective or retrospective, reporting the efficacy of stereoelectroencephalography-guided radiofrequency thermocoagulation (SEEG-RFTC) and/or MRgLITT in patients with drug-resistant epilepsy (DRE). Sample size ≥5. Reports the specific number of seizure-free patients and complications. Published in English. **Study exclusion criteria**	**Intervention details** MRgLITT **Comparator details** 2 MRgLITT studies compared MRgLITT with open resection and 1 with anterior temporal lobe resection, but comparator outcomes were not reported. The remainder had no comparator. The review also reported separately outcomes for	**Critical outcomes** f/u> 6 months *Seizure freedom (Engel class I)* n=414 (16 studies) (Note: this includes 83 patients with HH) Mean seizure free rate: 65% (95% CI 56 to 74) Seizure free range across studies: 46% to 93% Significant study heterogeneity (I^2=69.42 (p=0.00))	This study was appraised using the JBI critical appraisal checklist for systematic reviews and research synthesis. 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Unclear 7. No 8. Yes 9. Yes 10. NA 11. NA

Study location Beijing, China All included studies carried out in the USA **Study type** SRMA **Study aim** To undertake a meta-analysis to assess the effectiveness and safety of MRgLITT and/or SEEG-RFTC in treating drug-resistant epilepsy. **Study dates** Search to November 2019. Included studies were published in 2015-2019.	Case reports or reviews. Follow-up <six months. Conference abstracts without full text. MRgLITT and/or SEEG-RFTC used as a secondary procedure after failure of a prior operation. Overlapping populations across publications. Use of an optimized or self-modified (surgical) technology. **Total sample size** n=414 in 16 MRgLITT studies **Baseline characteristics** 11 studies included adults and children, 5 studies included children only. The overall age range was 0.4-74 years. Aetiologies included: Hypothalamic hamartoma (HH) *, n=83 in four studies Temporal lobe epilepsy (TLE), n=266 in 12 studies Focal cortical dysplasia (FCD), n=12 in two studies Tuberous sclerosis complex, n=5 in two studies Periventricular nodular heterotopias (PNH), n=5 in two studies No further details provided. *Outcomes for this group are reported in the separate RER (URN 2006a)	subjects undergoing SEEG-RFTC in 10 studies.	*Seizure freedom (Engel class I) by aetiology* TLE (n=266 in 12 studies) Mean seizure free rate: 59% (95% CI 53 to 65) Low study heterogeneity (I^2 =0.00, (p=0.83)) FCD (n=12 in two studies) Mean seizure free rate: 62% (95% CI 28 to 91) Tuberous sclerosis complex (n=5 in two studies) Mean seizure free rate: 66% (95% CI 15 to 100) PNH (n=5 in two studies) Mean seizure free rate: 40% (95% CI 0 to 90) **Important outcomes** None reported **Safety** *Postoperative side-effects*: n not stated, 13 studies Total: 27 (7%; 95% CI 4 to 11) comprising: Visual field deficit: 9 Neurologic deficit: 7 Inaccurate fibre placement or device malfunction: 4 Haemorrhage or oedema: 4 Optic neuritis: 2 Diabetes insipidus: 1	**Other comments:** This SRMA included observational studies only of patients with DRE with a mix of aetiologies. Decisions about study inclusion were made by two independent reviewers, but it was not stated whether data extraction was done by one or two reviewers. There was very limited information about patient clinical or demographic background. Duration of f/u for the patients included in the analysis was not stated. Seizure freedom was defined using the Engel scale. Risk of bias in the included studies was assessed using a standardised approach (MINORS, the methodological index for nonrandomized studies). The authors considered the quality of evidence from the included studies to be low due to the retrospective design, lack of blinding and lack of comparator. Risk of publication bias was assessed and considered to be low. The subgroup analyses by aetiology were not planned but carried out because of significant study heterogeneity across all the studies. **Source of funding:** The study was supported by the National Natural Science Foundation of China and

				Beijing Municipal Natural Science Foundation.
Widjaja E, Papastavros T, Sander B, Snead C, Pechlivanoglou P. Early economic evaluation of MRI-guided laser interstitial thermal therapy (MRgLITT) and epilepsy surgery for mesial temporal lobe epilepsy. PLoS ONE. 2019;14(11). **Study location** Canada **Study type** Cost-utility analysis **Study aim** To conduct an early economic evaluation of MRgLITT relative to epilepsy surgery in adults with drug resistant temporal lobe epilepsy from a healthcare payer perspective. **Study dates** Not stated.	**Study inclusion criteria** Adults with drug resistant temporal lobe epilepsy who have undergone the same pre-surgical diagnostic evaluation, and were deemed eligible for MRgLITT or epilepsy surgery. **Study exclusion criteria** NA **Total sample size** NA **Baseline characteristics** Hypothetical cohort. Average age 35.8 years (SD 1.2 years) (based on the age distribution from a population-based study of adults undergoing epilepsy surgery).	**Intervention details** MRgLITT **Comparator details** Epilepsy surgery (not further defined)	**Critical outcomes** None reported **Important outcomes** None reported **Cost-utility outcomes** *Life years* MRgLITT: 26.43 Surgery: 26.44 *Costs* MRgLITT: $165,303 Surgery: $157,482 *QALYs* MRgLITT: 24.7 Surgery: 24.62 *Incremental cost-effectiveness ratio*: $94,350 per QALY	**Comments:** All analyses were done from the Canadian healthcare payer perspective. Model inputs were taken from studies published between 1994 and 2019. Health states were seizure free or disabling seizures and probabilities for these and for deaths after MRgLITT or surgery used in the model were based on published data. These studies reported a higher probability of seizure freedom and a higher probability of death after surgery than after MRgLITT, but these findings were from separate studies and it is not clear how comparable the populations were. The probabilities of other outcomes (including neurological complications) were assumed to be the same after MRgLITT as surgery because of the lack of data available about MRgLITT. A discount rate of 1.5% was applied to both costs and health effects. The time period for costs used was not stated. Canadian costs were used and a cost-effectiveness threshold of $50,000/QALY was assumed. It is unclear how generalisable Canadian costs are to the NHS setting.

				In the base case MRgLITT yielded 0.08 more QALYs and cost $7,821 more than surgery. Sensitivity analyses were carried out and the model was sensitive to the probabilities of becoming seizure-free or returning to disabling seizures, the cost of MRgLITT disposable equipment, and the utilities of disabling seizures or seizure-free states after the procedure. Surgery was the preferred strategy in more than 50% of the sensitivity analysis iterations. **Source of funding:** The paper states 'the authors received no specific funding for this work'.
Xue F, Chen T, Sun H. Postoperative outcomes of magnetic resonance imaging (MRI)-guided laser interstitial thermal therapy (LITT) in the treatment of drug-resistant epilepsy: A meta-analysis. Medical Science Monitor. 2018;24:9292-9. http://dx.doi.org/10.12659/MSM.911848 **Study location** Tianjin, China. Included studies were carried out in USA (n=15) and Canada (n=1). **Study type** SRMA of observational studies	**Study inclusion criteria** Patients with epilepsy who were medication-resistant with focal onset of seizures All patients treated with MRgLITT, which was performed in a standard manner Contained comparable data that evaluated the efficacy of MRgLITT. Methodological Index for Non-Randomized Studies (MINORS) score of ≥13 (max possible score 16). Published in English. **Study exclusion criteria** Studies without crucial and assessable data for statistical analysis Non-original studies such as reviews, letters, and commentaries	**Intervention details** MRgLITT **Comparator details** No comparator	**Critical outcomes** F/u ranged from 7 days to 51 months across studies. 14 had f/u ≥3 months. *Seizure freedom: Engel outcome scale* Engel class I (n=189, 12 studies) Pooled prevalence: 61% (95% CI, 54 to 68) Range across studies: 41–88% Low study heterogeneity (I^2=14.5%; p=0.302). Engel Class II (n=135, 7 studies) Pooled prevalence: 12% (95% CI, 7 to 16) Range across studies: 3–65% Significant study heterogeneity (I^2=86.8%; p=0.000).	This study was appraised using the JBI critical appraisal checklist for systematic reviews and research synthesis. 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. No 7. Yes 8. Yes 9. No 10. NA 11. Yes **Other comments:** This SRMA include observational studies only, with patients with medication-

Study aim To undertake a systematic review of the literature with meta-analysis of the data from published studies to assess the effectiveness of MRI-guided laser interstitial thermal therapy in treatment-resistant epilepsy. **Study dates** Search to May 2018. Included studies were published in 2012-2018.	**Total sample size** n=189 in 12 studies **Baseline characteristics** Age range 1-69 years across studies. Four studies included adults and children, one included adults only, the remainder did not report the age range of included subjects. Underlying conditions were: Mesial temporal lobe epilepsy (5 studies), Temporal lobe epilepsy (3 studies), Lesional and localised epilepsy (3 studies), Insular epilepsy (1 study).		Engel Class II (n=115, 6 studies, excluding Grewal et al) Pooled prevalence: 6% (no CI reported) Range across studies: 3–23% Low study heterogeneity (I^2=26.9%; p=0.242). Engel Class III (n=135, 6 studies) Pooled prevalence: 18% (95% CI, 10 to 22) Range across studies: 9–27% Low study heterogeneity (I^2=3.0%; p=0.397). Engel Class IV (n=109, 5 studies) Pooled prevalence: 15% (95% CI, 8 to 22), Range across studies: 9–27% Low study heterogeneity (I^2=13.2%; p=0.330). **Important outcomes** None reported **Safety** *Post-operative complications* (n=101, 7 studies) Pooled prevalence: 24% (95% CI, 16 to 32) Range across studies: 15–43% Low study heterogeneity (I^2=0%; p=0.629).	resistant focal epilepsy due different aetiologies. There was limited information about patient clinical or demographic background. Around three-quarters of all patients included in the analyses had temporal lobe epilepsy. Risk of bias in the included studies was assessed using a standardised approach (MINORS) and studies with a higher risk of bias were excluded. Data extraction was done by only one reviewer, but was checked by a second reviewer. The authors reported that all included studies used prospectively collected data. Seizure freedom was defined using the Engel scale. **Source of funding:** No comment on source of funding
Abbreviations: AED: anti-epileptic drug; BVMT-R: Brief Visual Memory Test–Revised; COWAT: Controlled Oral Word Association Test; Dom: language dominant hemisphere; DRE: drug-resistant epilepsy; f/u: follow-up; EEG: electroencephalogram; FCD: Focal cortical dysplasia; HH: Hypothalamic hamartoma; LAANTERN: Laser Ablation of Abnormal Neurological Tissue Using Robotic NeuroBlate System; MINORS: Methodological Index for Non-Randomized Studies; mTLE: mesiotemporal epilepsy; MSE: mesial temporal sclerosis epilepsy; MTLE: Mesial temporal lobe epilepsy; MTS: mesial temporal sclerosis; NA: not applicable; Non-dom: non-dominant hemisphere; ns: not significant; PNH: Periventricular nodular heterotopias; QALY: Quality-adjusted life year; RAVLT: Rey auditory verbal learning test; SD: standard deviation; SEEG: stereoencephalography; SEEG-RFTC: stereoelectroencephalography guided radiofrequency thermocoagulation; SLAH: stereotactic laser amygdalohippocampotomy; SRMA: systematic review and meta-analysis; SRS: stereotactic radiosurgery; TLE: Temporal lobe epilepsy;				

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for Systematic Reviews and Research Synthesis

1. Is the review question clearly and explicitly stated?
2. Were the inclusion criteria appropriate for the review question?
3. Was the search strategy appropriate?
4. Were the sources and resources used to search for studies adequate?
5. Were the criteria for appraising studies appropriate?
6. Was critical appraisal conducted by two or more reviewers independently?
7. Were there methods to minimize errors in data extraction?
8. Were the methods used to combine studies appropriate?
9. Was the likelihood of publication bias assessed?
10. Were recommendations for policy and/or practice supported by the reported data?
11. Were the specific directives for new research appropriate?

JBI Critical Appraisal Checklist for Case Series

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series?
3. Were valid methods used for the identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?

JBI Critical Appraisal Checklist for Cohort Studies

1. Were the two groups similar and recruited from the same population?
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?
3. Was the exposure measured in a valid and reliable way?
4. Were confounding factors identified?
5. Were strategies to deal with confounding factors stated?
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?

7. Were the outcomes measured in a valid and reliable way?
8. Was the follow-up time reported and sufficient to be long enough for outcomes to occur?
9. Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored?
10. Were strategies to address incomplete follow-up utilized?
11. Was appropriate statistical analysis used?

Appendix G GRADE profiles

Table 1: Question: 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?

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study type and number of studies Author year	Risk of bias	Indirectness	Inconsistency	Imprecision	MRgLITT	Open resection	Result (95% CI)		
Seizure freedom. For seizure freedom, higher rates of Engel class I seizures are better.									
Seizure outcomes, Engel Class I to IV (6 months f/u)									
1 cohort study Drane et al 2015	Serious limitations [1]	No serious indirectness	Not applicable	Not calculable	n=10 with TLE, procedure on dominant hemisphere	n=22 with TLE, procedure on dominant hemisphere	MRgLITT; open resection Engel I: 7/10; 11/22 Engel II: 1/10; 5 /22 Engel III: 2/10; 3/22 Engel IV: 0/10; 3/22	Critical	Very low
1 cohort study Drane et al 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n=9 with TLE, procedure on non-dominant hemisphere	n=17 with TLE, procedure on non-dominant hemisphere	MRgLITT; open resection Engel I: 4/9; 13/17 Engel II: 0/9; 2/17 Engel III: 2/9; 2/17 Engel IV: 3/9; 0/17	Critical	Very low
Mean seizure free rate (Engel class I) [A] (>6 months f/u)									
1 SRMA of 16 case series Wang et al 2020	Serious limitations [2]	Serious indirectness [3]	Serious inconsistency [4]	Not calculable	n=414 with various aetiologies (including n=83 with HH)	No comparator	65% (95% CI 56 to 74) I^2=69.42 (p=0.00)	Critical	Very low
Mean seizure free rate (Engel class I) (>6 months f/u)									
1 SRMA of 12 case series	Serious limitations [2]	Serious indirectness [3]	No serious inconsistency	Not calculable	n=266 with TLE	No comparator	59% (95% CI 53 to 65) I^2 =0.00, (p=0.83)	Critical	Very low

Wang et al 2020									
Mean seizure free rate (Engel class I) (>6 months f/u)									
1 SRMA of 2 case series Wang et al 2020	Serious limitations [2]	Serious indirectness [3]	Not applicable	Not calculable	n=12 with FCD	No comparator	62% (95% CI 28 to 91)	Critical	Very low
Mean seizure free rate (Engel class I) (>6 months f/u)									
1 SRMA of 2 case series Wang et al 2020	Serious limitations [2]	Serious indirectness [3]	Not applicable	Not calculable	n=5 with tuberous sclerosis complex	No comparator	66% (95% CI 15 to 100)	Critical	Very low
Mean seizure free rate (Engel class I) [A] (>6 months f/u)									
1 SRMA of 2 case series Wang et al 2020	Serious limitations [2]	Serious indirectness [3]	Not applicable	Not calculable	n=5 with PNH	No comparator	40% (95% CI 0 to 90)	Critical	Very low
Freedom from disabling seizures (not defined) (mean 8.3 +/- 1.27 months f/u)									
1 case series Bermudez et al 2020	Very serious limitations [5]	Serious indirectness [6]	Not applicable	Not calculable	n=13, MTLE, surgery on dominant hemisphere	No comparator	85% (11/13) No CI reported	Critical	Very low
Freedom from disabling seizures (not defined) (mean 8.5 +/- 4.6 months f/u)									
1 case series Bermudez et al 2020	Very serious limitations [5]	Serious indirectness [6]	Not applicable	Not calculable	n=13, MTLE, surgery on non-dominant	No comparator	75% (10/13) No CI reported	Critical	Very low

					hemisphere				
Seizure freedom (Engel class I) (12-month f/u after first procedure)									
1 case series Gross et al 2018	Serious limitations [2]	Serious indirectness [6]	Not applicable	Not calculable	n=58 with MTLE	No comparator	48.3% (95% CI 35.9 to 50.8)	Critical	Very low
Seizure freedom (Engel class I) (12-month f/u after first procedure)									
1 case series Gross et al 2018	Serious limitations [2]	Serious indirectness [6]	Not applicable	Not calculable	n=43 with MTLE with MTS	No comparator	58.1% (95% CI 43.3 to 71.6)	Critical	Very low
Seizure freedom (Engel class I) (12-month f/u after first procedure)									
1 case series Gross et al 2018	Serious limitations [2]	Serious indirectness [6]	Not applicable	Not calculable	n=15 with MTLE without MTS	No comparator	20.0% (95% CI 6.3 to 46.0)	Critical	Very low
Seizure outcomes, Engel Class I to IV (12-month f/u after the latest procedure)									
1 case series Gross et al 2018	Very serious limitations [7]	Serious indirectness [6]	Not applicable	Not calculable	n=58 with MTLE	No comparator	I: 31* (53.4% (95% CI 40.8 to 65.7)) II: 13 (22.4%) III: 11 (19.0% IV: 3 (5.2%) *Of whom IA: 22; IB: 7; ID: 2.	Critical	Very low
Seizure outcomes, Engel Class I to IV (12-month f/u after the latest procedure)									
1 case series Gross et al 2018	Very serious limitations [7]	Serious indirectness [6]	Not applicable	Not calculable	n=43 with MTLE with MTS	No comparator	I: 26 (60.5% (95% CI 45.6 to 73.7)) II: 10 (23.2%) III: 7 (16.3%) IV: 0	Critical	Very low

Seizure outcomes, Engel Class I to IV (12-month f/u after the latest procedure)									
1 case series Gross et al 2018	Very serious limitations [7]	Serious indirectness [6]	Not applicable	Not calculable	n=15 with MTLE without MTS	No comparator	I: 5 (33.3% (95% CI 15.0 to 58.5)) II: 3 (20.0%) III: 4 (26.7%) IV: 3 (20.0%)	Critical	Very low
Seizure freedom (Engel class I) at 24 months after the latest procedure (Kaplan-Meier analysis)									
1 case series Gross et al 2018	Serious limitations [2]	Serious indirectness [6]	Not applicable	Not calculable	n=58 with MTLE	No comparator	34.3% (95% CI 19.7 to 49.3)	Critical	Very low
Seizure outcomes, Engel Class I to IV (12-month f/u)									
1 case series Landazuri et al 2020	Very serious limitations [7]	Very serious indirectness [6]	Not applicable	Not calculable	n=42 with various aetiologies	No comparator	I: 27/42, 64.3% (95% CI 48.0 to 78.5) II: 4/42, 9.5% (no CI reported) III: 9/42, 21.4% (no CI reported) IV: 2/42, 4.8% (95% CI 0.6 to 16.2)	Critical	Very low
Seizure outcomes, Engel Class I to IV (12-month f/u)									
1 case series Landazuri et al 2020	Very serious limitations [7]	Very serious indirectness [6]	Not applicable	Not calculable	n=24 with MTLE/MSE	No comparator	I: 17/24, 70.8 % (95% CI 48.9 to 87.4) II: 3/24, 12.5% (no CI reported) III: 4/24, 16.7% (no CI reported) IV: 0	Critical	Very low
Seizure outcomes, Engel Class I to IV (12-month f/u)									
1 case series Landazuri et al 2020	Very serious limitations [7]	Very serious indirectness [6]	Not applicable	Not calculable	n=18 with non-MTLE/MSE	No comparator	I: 10/18, 55.6% (95% CI 30.8 to 78.5) II: 1/18, 5.6% (no CI reported) III: 5/18, 27.8% (no CI reported) IV: 2/18, 11.1% (no CI reported)	Critical	Very low
Seizure freedom (Engel class IA +/- IB (12 to 36 months f/u)									
1 SRMA of 9 case series	Serious limitations [2]	Serious indirectness [3]	No serious inconsistency	Not calculable	n=250 with TLE	No comparator	Mean incidence 50%, (95% CI 44 to 56) I^2 =0.00, p=0.78	Critical	Very low

Sanjeet et al 2019									
Seizure outcome (Engel class I) (f/u range 7 days to 51 months)									
1 SRMA of 12 case series Xue et al 2018	No serious limitations	Serious indirectness [3]	No serious inconsistency	Not calculable	n=189 with various aetiologies	No comparator	Pooled prevalence: 61% (95% CI 54 to 68) I^2=14.5%; p=0.302	Critical	Very low
Seizure outcome (Engel class II) (f/u range 7 days to 51 months)									
1 SRMA of 7 case series Xue et al 2018	No serious limitations	Serious indirectness [3]	Serious inconsistency [4]	Not calculable	n=135 with various aetiologies	No comparator	Pooled prevalence: 12% (95% CI 7 to 16) I^2=86.8%; p=0.000	Critical	Very low
Seizure outcome (Engel class III) (f/u range 7 days to 51 months)									
1 SRMA of 6 case series Xue et al 2018	No serious limitations	Serious indirectness [3]	No serious inconsistency	Not calculable	n=135 with various aetiologies	No comparator	Pooled prevalence: 18% (95% CI 10 to 22) I^2=3.0%; p=0.397	Critical	Very low
Seizure outcome (Engel class IV) (f/u range 7 days to 51 months)									
1 SRMA of 5 case series Xue et al 2018	No serious limitations	Serious indirectness [3]	No serious inconsistency	Not calculable	n=109 with various aetiologies	No comparator	Pooled prevalence: 15% (95% CI 8 to 22), I^2=13.2%; p=0.330	Critical	Very low
Neuropsychological outcomes. For neuropsychological outcomes, higher rates or scores are better.									
Boston Naming Test (mean score (SD) at baseline; mean (SD) change in score), (higher score better) (6 month or 1 year f/u)									
1 cohort study	Very serious limitations[8]	No serious indirectness	Not applicable	Not calculable	n=10 with TLE, procedure on	n=22 with TLE, procedure	*Boston Naming Test* SLAH: 70.3 (22.4); 8.6 (25.7) Open resection: 76.6 (14.5); -23.6** (17.6)	Critical	Very low

Drane et al 2015					dominant hemisphere	on dominant hemisphere	(SLAH at 6 months; open resection at 1 year) **significantly different from dominant SLAH and both non-dominant groups (see row below), p<0.01		
1 cohort study Drane et al 2015	Very serious limitations[8]	No serious indirectness	Not applicable	Not calculable	n=9 with TLE, procedure on non-dominant hemisphere	n=17 with TLE, procedure on non-dominant hemisphere	SLAH: 85.6 (11.1); 3.2 (3.7) Open resection: 92.7 (7.0); 1.9 (4.8) (SLAH at 6 months; open resection at 1 year)	Critical	Very low
Famous face naming (mean score (SD) at baseline; mean (SD) change in score), (higher score better) (6 month or 1 year f/u)									
1 cohort study Drane et al 2015	Very serious limitations[8]	No serious indirectness	Not applicable	Not calculable	n=10 with TLE, procedure on dominant hemisphere	n=22 with TLE, procedure on dominant hemisphere	*Famous face naming* SLAH: 67.0 (23.6); 9.4 (12.5) Open resection: 69.9 (21.2); -28.3** (30.5) (SLAH at 6 months; open resection at 1 year) **significantly different from dominant SLAH and both non-dominant groups (see row below), p<0.01	Critical	Very low
1 cohort study Drane et al 2015	Very serious limitations[8]	No serious indirectness	Not applicable	Not calculable	n=9 with TLE, procedure on non-dominant hemisphere	n=17 with TLE, procedure on non-dominant hemisphere	SLAH: 89.9 (6.0); 7.6 (12.6) Open resection: 89.7 (6.9); 1.4 (8.1) (SLAH at 6 months; open resection at 1 year)	Critical	Very low
Famous face recognition naming (mean score (SD) at baseline; mean (SD) change in score), (higher score better) (6 month or 1 year f/u)									
1 cohort study	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n=10 with TLE, procedure	n=22 with TLE, procedure	SLAH: 72.9 (16.7); 4.2 (5.5) Open resection: 66.1 (15.2); 0.5 (13.2)	Critical	Very low

Drane et al 2015					on dominant hemisphere	on dominant hemisphere	(SLAH at 6 months; open resection at 1 year)		
1 cohort study Drane et al 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n=9 with TLE, procedure on non-dominant hemisphere	n=17 with TLE, procedure on non-dominant hemisphere	SLAH: 74.0 (16.6); 5.0 (4.9) Open resection: 76.0 (18.8); -9.0*** (16.5) (SLAH at 6 months; open resection at 1 year) ***significantly different from non-dominant SLAH and both dominant groups (see row above), p<0.001	Critical	Very low
RAVLT (Mean score +/- SD (range)) (higher score better), (f/u average 6.4 (+/- 1.5) months (range 5-11 months))									
1 case series Gross et al 2018	Very serious limitations [5]	Serious indirectness [6]	Not applicable	Not calculable	n=49 with MTLE	No comparator	RAVLT-learning Pre: 41.8 +/- 10.8 (14 to 65) F/u: 41.9 +/- 11.6 (11 to 59) ns RAVLT-Delayed recall Pre: 5.9 +/- 3.9 (0 to 15) F/u: 6.5 +/- 4.1 (0 to 14) ns	Critical	Very low
RAVLT (Mean score +/- SD (range)) (higher score better), (f/u average 6.4 (+/- 1.5) months (range 5-11 months))									
1 case series Gross et al 2018	Very serious limitations [5]	Serious indirectness [6]	Not applicable	Not calculable	n=20 with MTLE, dominant hemisphere SLAH	No comparator	RAVLT learning Pre: 37.4 +/- 10.7 (14 to 62) F/u: 35.3 +/- 12.7 (11 to 56) ns RAVLT delayed recall Pre: 4.6 +/- 3.7 (0 to 13) F/u: 4.2 +/- 3.4 (1 to 12) ns	Critical	Very low
RAVLT (Mean score +/- SD (range)) (higher score better), (f/u average 6.4 (+/- 1.5) months (range 5-11 months))									
1 case series	Very serious limitations [5]	Serious indirectness [6]	Not applicable	Not calculable	n=29 with MTLE, non-dominant	No comparator	RAVLT learning Pre: 44.9 +/- 10.0 (33 to 65) F/u: 46.6 +/- 8.3 (22 to 59) ns	Critical	Very low

Gross et al 2018					hemisphere SLAH		RAVLT delayed recall Pre: 6.6 +/- 3.9 (1 to 15) F/u: 8.2 +/- 3.7 (0 to 14) p<0.05		
Wechsler memory scale (mean (SD) score: higher score better) (mean follow-up 8.4 months (+/- 3.3 months))									
1 case series Bermudez et al 2020	Very serious limitations [5]	Serious indirectness [6]	Not applicable	Not calculable	n=10 MTLE, surgery on dominant hemisphere	No comparator	Pre: 43.6 (13.9) F/u: 41.7 (13.4)	Critical	Very low
Wechsler memory scale (mean (SD) score: higher score better) (mean follow-up 8.4 months (+/- 3.3 months))									
1 case series Bermudez et al 2020	Very serious limitations [5]	Serious indirectness [6]	Not applicable	Not calculable	n=6 MTLE, surgery on non-dominant hemisphere	No comparator	Pre: 45.3 (10.9) F/u: 48.8 (3.4)	Critical	Very low
List learning (mean % learned (SD) and mean % retained (SD): higher % better) (mean follow-up 8.4 months (+/- 3.3 months))									
1 case series Bermudez et al 2020	Very serious limitations [5]	Serious indirectness [6]	Not applicable	Not calculable	n=10 MTLE, surgery on dominant hemisphere	No comparator	% learned Pre: 57.0% (12.1) F/u 57.2% (13.1) % retained Pre: 47.3% (19.2) F/u: 39.8% (25.9)	Critical	Very low
List learning (mean % learned (SD) and mean % retained (SD): higher % better) (mean follow-up 8.4 months (+/- 3.3 months))									
1 case series Bermudez et al 2020	Very serious limitations [5]	Serious indirectness [6]	Not applicable	Not calculable	n=9 MTLE, surgery on non-dominant hemisphere	No comparator	% learned Pre: 58.7% (18.5) F/u: 66.9% (14.6) % retained Pre: 62.0% (21.2) F/u: 73.2% (14.6)	Critical	Very low

Brief Visual Memory Test–Revised, mean total T-score (SD) (higher score better): (mean follow-up 8.4 months (+/- 3.3 months))									
1 case series Bermudez et al 2020	Very serious limitations [5]	Serious indirectness [6]	Not applicable	Not calculable	n=8 MTLE, surgery on dominant hemisphere	No comparator	Pre: 35.7 (10.6) F/u: 38.3 (13.9)	Critical	Very low
Brief Visual Memory Test–Revised, mean total T-score (SD) (higher score better): (mean follow-up 8.4 months (+/- 3.3 months))									
1 case series Bermudez et al 2020	Very serious limitations [5]	Serious indirectness [6]	Not applicable	Not calculable	n=8 MTLE, surgery on non-dominant hemisphere	No comparator	Pre: 31.8 (12.9) F/u: 35.9 (12.1)	Critical	Very low
Naming (mean % correct) (SD) (higher score better): (mean follow-up 8.4 months (+/- 3.3 months))									
1 case series Bermudez et al 2020	Very serious limitations [5]	Serious indirectness [6]	Not applicable	Not calculable	n=11 MTLE, surgery on dominant hemisphere	No comparator	Pre: 63.3% (14.7) F/u: 60.5% (20.4)	Critical	Very low
Naming (mean % correct) (SD) (higher score better): (mean follow-up 8.4 months (+/- 3.3 months))									
1 case series Bermudez et al 2020	Very serious limitations [5]	Serious indirectness [6]	Not applicable	Not calculable	n=10 MTLE, surgery on non-dominant hemisphere	No comparator	Pre: 68.9% (16.8) F/u: 72.2% (16.6)	Critical	Very low
Controlled Oral Word Association Test (verbal fluency) mean score (SD) (higher score better): (mean follow-up 8.4 months (+/- 3.3 months))									
1 case series Bermudez et al 2020	Very serious limitations [5]	Serious indirectness [6]	Not applicable	Not calculable	n=11 MTLE, surgery on dominant hemisphere	No comparator	Phonemic T-score Pre: 41.1 (11.8) F/u: 44.9 (12.5) Semantic T-score Pre: 40.6 (11.8) F/u: 39.4 (9.9)	Critical	Very low

Controlled Oral Word Association Test (verbal fluency) mean score (SD) (higher score better): (mean follow-up 8.4 months (+/- 3.3 months))									
1 case series Bermudez et al 2020	Very serious limitations [5]	Serious indirectness [6]	Not applicable	Not calculable	n=9 MTLE, surgery on non-dominant hemisphere	No comparator	Phonemic T score Pre: 42.4 (18.0) F/u: 50.3 (10.7) Semantic T score Pre: 44.0 (9.8) F/u: 39.8 (9.5)	Critical	Very low
Trails A (processing speed) mean T score (SD) (higher score better): (mean follow-up 8.4 months (+/- 3.3 months))									
1 case series Bermudez et al 2020	Very serious limitations [5]	Serious indirectness [6]	Not applicable	Not calculable	n=9 MTLE, surgery on dominant hemisphere	No comparator	Pre: 35.8 (10.9) F/u: 40.0 (10.3)	Critical	Very low
Trails A (processing speed) mean T score (SD) (higher score better): (mean follow-up 8.4 months (+/- 3.3 months))									
1 case series Bermudez et al 2020	Very serious limitations [5]	Serious indirectness [6]	Not applicable	Not calculable	n=6 MTLE, surgery on non-dominant hemisphere	No comparator	Pre: 32.8 (4.0) F/u: 46.2 (8.7)	Critical	Very low
Grooved pegboard test (fine motor dexterity) mean T score (SD) (higher score better): (mean follow-up 8.4 months (+/- 3.3 months))									
1 case series Bermudez et al 2020	Very serious limitations [5]	Serious indirectness [6]	Not applicable	Not calculable	n=11 MTLE, surgery on dominant hemisphere	No comparator	Pre: 36.5 (8.8) F/u: 38.9 (8.7)	Critical	Very low
Grooved pegboard test (fine motor dexterity) mean T score (SD) (higher score better): (mean follow-up 8.4 months (+/- 3.3 months))									
1 case series Bermudez et al 2020	Very serious limitations [5]	Serious indirectness [6]	Not applicable	Not calculable	n=7 MTLE, surgery on non-dominant hemisphere	No comparator	Pre: 36.0 (9.2) F/u: 41.7 (10.1)	Critical	Very low

Quality of Life For QOLIE scores, higher rates or scores are better.									
QOLIE-31 [B] score (median (range); higher score better) at baseline and latest f/u (duration of f/u not stated)									
1 case series Landazuri et al 2020	Very serious limitations [9]	Very serious indirectness [6]	Not applicable	Not calculable	n=29 with various aetiologies	No comparator	Baseline: 51.7 (range 8.7 to 77.3) Last f/u: 65.8 (range not stated) p=0.2173	Critical	Very low
QOLIE-31 score: median improvement in QOLIE subscore from baseline to latest f/u (duration of f/u not stated)									
1 case series Landazuri et al 2020	Very serious limitations [9]	Very serious indirectness [5]	Not applicable	Not calculable	n=29 with various aetiologies	No comparator	Seizure worry: +15 (p=0.0219) Emotional wellbeing: +8 (ns) Energy/ fatigue: +5 (ns) Cognitive function: +7 (ns) Social functioning: +15 (p=0.0175) (ns: not significant)	Critical	Very low
Hospitalisations									
Rehospitalisation within 90 days									
1 case series Landazuri et al 2020	Very serious limitations [10]	Very serious indirectness [6]	Not applicable	Not calculable	n not stated, various aetiologies	No comparator	1 patient	Important	Very low
Safety. For safety outcomes, lower rates or numbers are better.									
Post-operative side-effects									
1 SRMA of 13 case series Wang et al 2020	Serious limitations [2]	Serious indirectness [3]	Not applicable	Not calculable	n not stated, various aetiologies	No comparator	Total: 27 (7%; 95% CI 4 to 11) Comprising: Visual field deficit: 9 Neurologic deficit: 7 Inaccurate fibre placement or device malfunction: 4 Haemorrhage or oedema: 4 Optic neuritis: 2 Diabetes insipidus: 1	Important	Very low

Post-operative complications									
1 SRMA of 7 case series Xue et al 2018	No serious limitations	Serious indirectness [3]	No serious inconsistency	Not calculable	n=101 with various aetiologies	No comparator	Pooled prevalence: 24% (95% CI, 0.16 to 0.32) Range across studies: 15–43% (I^2=0%; p=0.629).	Important	Very low
Complications (12-month f/u)									
1 case series Gross et al 2018	Very serious limitations [7]	Serious indirectness [6]	Not applicable	Not calculable	n=58 with MTLE	No comparator	Visual field deficit: 5/58 (8.6%), of which one (1.7%) was persistent and symptomatic.	Important	Very low
Procedure-related adverse events (12-month f/u)									
1 case series Landazuri et al 2020	Very serious limitations [7]	Very serious indirectness [6]	Not applicable	Not calculable	n=60 with various aetiologies	No comparator	5/60 (8.3%), of which: 'Not serious': 4 'Serious': 1	Important	Very low
Complication rate (Median f/u 22.4 months (range 7-70 months))									
1 SRMA of 8 case series Sanjeet et al 2019	Serious limitations [2]	Serious indirectness [3]	No serious inconsistency	Not calculable	n=207 with TLE	No comparator	Overall complication rate 20% (95% CI 14 to 26) I^2 =0.00, p=0.63 Including: Visual field deficits: n=12 Cranial nerve deficits: n=8 Headache, nausea, and gait abnormalities: n=9 Cerebral haemorrhage: n=4	Important	Very low
Reoperations (mean reoperation rate) (Median f/u 22.4 months (range 7-70 months))									
1 SRMA of 7 case series Sanjeet et al 2019	Serious limitations [2]	Serious indirectness [3]	No serious inconsistency	Not calculable	n=184 with TLE	No comparator	Mean reoperation rate: 15% (95% CI 9 to 22) I^2 =19.87, p=0.28	Important	Very low

Abbreviations:
CI: Confidence intervals; Dom: language dominant hemisphere; FCD: focal cortical dysplasia; f/u: follow-up; HH: hypothalamic hamartoma; MSE: mesial temporal sclerosis epilepsy; MTLE: mesial temporal lobe epilepsy; MTS: mesial temporal sclerosis; Non-dom: non-dominant hemisphere; ns: not significant; PNH: periventricular nodular heterotopia; Pre: pre-operative; RAVLT: Rey auditory verbal learning test; SD: standard deviation; SLAH: stereotactic laser amygdalohippocampotomy; SRMA: systematic review and meta-analysis; TLE: temporal lobe epilepsy;

1. Serious risk of bias due to lack of statistical analysis
2. Serious risk of bias due to unclear reporting of study participants.
3. Serious indirectness as only non-comparative evidence was identified for inclusion in this SRMA.
4. Serious inconsistency due to study heterogeneity.
5. Very serious risk of bias due to unclear reporting of study participants, loss to f/u, and lack of statistical analysis.
6. Serious indirectness due to lack of comparator.
7. Very serious risk of bias due to unclear reporting of study participants and lack of statistical analysis for some or all outcomes.
8. Very serious risk of bias due to baseline differences in scores between groups and lack of statistical analysis for some or all outcomes
9. Very serious risk of bias due to unclear reporting of study participants and loss to f/u.
10. Very serious risk of bias due to unclear reporting of study participants, lack of statistical analysis and no reporting of n included in outcome.

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 QOLIE-31: The QOLIE-31 includes 39 items in 6 sections: energy, emotional wellbeing, activities/ social, cognitive function, seizure worry, effects of medication; as well as two items about overall QOL and overall health.

Glossary

Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether the event is suspected to be related to or caused by the drug, treatment or intervention.
Baseline	The set of measurements at the beginning of a study (after any initial 'run-in' period with no intervention), with which subsequent results are compared.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.
Blinding	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias.
Case series	Reports of several patients with a given condition, usually covering the course of the condition and the response to treatment. There is no comparison (control) group of patients.
Clinical importance	A benefit from treatment that relates to an important outcome such as length of life and is large enough to be important to patients and health professionals.
Confidence interval	A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval (CI) indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow CI indicates a more precise estimate (for example, if a large number of patients have been studied). The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that 'based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110'. In such a case the 95% CI would be 110 to 150.
Control group	A group of people in a study who do not have the intervention or test being studied. Instead, they may have the standard intervention. The results for the control group are compared with those for a group having the intervention being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as possible to those in the intervention group, to make it as easy as possible to detect any effects due to the intervention.
Cost effectiveness study	An analysis that assesses the cost of achieving a benefit by different means. The benefits are expressed in non-monetary terms related to health, such as life years gained (that is, the number of years by which life is extended as a result of the intervention). Options are often compared on the cost incurred to achieve 1 outcome (for example, cost life year gained).
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future.

	Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
Incremental cost-effectiveness ratio (ICER)	The difference in the change in mean costs in the population of interest divided by the difference in the change in mean outcomes in the population of interest.
Meta-analysis	A method often used in systematic reviews to combine results from several studies of the same test, treatment or other intervention to estimate the overall effect of the treatment.
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).
Prospective study	A research study in which the health or other characteristic of patients is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
P-value (p)	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Quality-adjusted life year (QALY)	A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life, and freedom from pain and mental disturbance.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Standard deviation	A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.

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