National Institute for Health and Care Excellence

FINAL

Epilepsies in children, young people and adults: diagnosis and management

[13] Evidence reviews for surgery: referral and surgical interventions

NICE guideline NG217

Evidence review underpinning recommendations 8.2.1 to 8.2.4 in the NICE guideline

April 2022

FINAL

Developed by the National Guideline Centre

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1 Resective epilepsy surgery

1.1 Introduction

Epilepsy surgery refers to a neurosurgical procedure where the primary purpose is to improve seizure control. Epilepsy surgery may be a viable treatment option for some people with seizures. Presurgical investigations are extensive and multidisciplinary, as is the post-surgical follow-up of people who undergo this procedure. 'Success' may be determined on an individual basis; freedom from seizures may be a goal for some; for others surgery may be offered as a palliative procedure. This chapter examines:

i) the evidence for the clinical and cost-effectiveness of different criteria for referral to surgery
ii) the evidence for the clinical and cost-effectiveness of resective epilepsy surgery (please see separate review for vagal nerve stimulation) .

1.2 Review question: What is the clinical and cost-effectiveness of different criteria for referral to epilepsy surgical services?

1.2.1 Summary of the protocol

Table 1: PICO characteristics of review question

Population	Inclusion: all children, young people and adults with epilepsy. Exclusion: new-born babies (under 28 days).
Interventions	Any referral criteria that have been evaluated. Strata: None.
Comparison	Other referral criteria.
Outcomes	Appropriateness of referral decisions.
Study design	RCTs. If no RCTs are found, non-randomised comparisons will be sought. If so, these papers will need to demonstrate that consideration has been made for any potential confounders.

1.2.2 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document. Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.2.3 Effectiveness evidence

No relevant studies were found

1.2.3.1 Included studies

No relevant clinical studies comparing different referral criteria in terms of the pre-determined outcome were identified.

See also the study selection flow chart in Appendix C, study evidence tables in Appendix H, forest plots in 0 and GRADE tables in Appendix J.

1.2.3.2 Excluded studies

See the excluded studies list in Appendix G.

1.2.4 Economic evidence

1.2.4.1 Included studies

No health economic studies were included.

1.2.4.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in D.

1.2.5 Economic model

This area was not prioritised for a new cost-effectiveness analysis.

1.2.6 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 2: Costs of pre-surgical evaluation tests

Resource	Unit costs	Source
History and examination	£240	NHS reference costs 2019/20. Currency code: WF01B Consultant led, Non-Admitted Face-to-Face Attendance, First, Service code 400,
Videotelemetry	£2,791	Currency code: AA80Z, Elective
Neuropsychology assessment	£334	Currency code: AA32Z, Outpatient procedures
Neuropsychiatry assessment	£346	NHS reference costs 2019/20. Currency code: WF01B Consultant-led, Non-Admitted Face-to-Face Attendance, First, Service code 656
MRI	£146	NHS reference costs 2019/20. Currency code: RD01A Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over
PET	£666	NHS reference costs 2019/20. Currency code RN01A Positron Emission Tomography with Computed Tomography (PET-CT) of One Area, 19 years and over

Resource	Unit costs	Source
Occupational therapy	£111	NHS reference costs 2019/20. Currency code WF01B Consultant led, Non-Admitted Face-to-Face Attendance, First, Service code 651
Physiotherapy	£59	NHS reference costs 2019/20. Currency code WF01B Consultant led, Non-Admitted Face-to-Face Attendance, First, Service code 650
sEEG	£14,638	NHS reference costs 2019/20. Currency code: Currency code AA83Z Elective Intracranial Telemetry
SPECT	£342	NHS reference costs 2019/20. Currency code RN04A Single Photon Emission Computed Tomography with Computed Tomography (SPECT-CT) of One Area, 19 years and over
fMRI	£146	Committee opinion (the same cost for MRI)
Amytal testing	£3,545	Committee opinion
MEG	£2,000 - £4,500	Committee opinion
ECoG	£3,000 - £5,000	Committee opinion
Multidisciplinary team meeting	£250	NHS reference costs 2019/20. Currency code: WF02B Consultant led, Multi-professional Non-Admitted Face-to-Face Attendance, First, Service code 150
Pre-surgical counselling	£346	NHS reference costs 2019/20. Currency code: WF01B Consultant-led, Non-Admitted Face-to-Face Attendance, First, Service code 656
Informed consent assessment	£224	NHS reference costs 2019/20. Currency code: WF01B, Consultant led, Non-Admitted Face-to-Face Attendance, First, Service code 150

Source: NHS reference costs 2019/20 [42] and committee opinion

Costs for epilepsy surgery were found by looking up OPCS codes for the epilepsy surgery types listed on the review protocol. These were then linked to the HRG codes using the HRG4 reference costs grouper ‘code to group’ spreadsheet. A single OPCS code can be linked to several HRG codes depending on whether certain ‘flags’ are raised that changes the complexity of the procedure. All the codes HRG codes identified are listed below for an illustration of the costs.

Table 3: Costs of surgery

Resource	Unit costs	Activity	Source
AA50A, AA50B, AA50C Very Complex Intracranial Procedures, 19 years and over. Weighted average of CC scores 0-5, 6-11 and 12+	£15,940	656	NHS reference costs 2018/19
AA51A, AA51B , AA51C, AA51D Complex Intracranial Procedures, 19 years and over. Weighted average of CC scores 0-3, 4-7, 8-11, and 12+	£9,975	2,067	
AA52A, AA52B , AA52C, AA52D Very Major Intracranial Procedures, 19 years and over. Weighted average of CC scores 0-3, 4-7, 8-11, and 12+	£9,020	3,230	
AA53A, AA53B, AA53C, AA53D Major Intracranial Procedures, 19 years and over. Weighted average of CC scores 0-3, 4-7, 8-11, and 12+	£7,504	3,925	

Resource	Unit costs	Activity	Source
AA50D, AA50E, AA50F Very Complex Intracranial Procedures, 18 years and under. Weighted average of CC scores 0-5, 6-11, and 12+	£14,010	176	
AA51E, AA51F, AA51G Complex Intracranial Procedures, 18 years and under. Weighted average of CC scores 0-3, 4-7, and 8+	£10,093	405	
AA52E, AA52F, AA52G Very Major Intracranial Procedures, 18 years and under. Weighted average of CC scores 0-3, 4-7, and 8+	£8,020	458	
AA53E, AA53F, AA53G Major Intracranial Procedures, 18 years and under. Weighted average of CC scores 0-3, 4-7, and 8+	£7,440	554	

Source: NHS reference costs 2019/20 [42]

Table 4: Anti-seizure medication costs

Drug[(a)]	Preparation	Mg/day[(b)]	Cost per year (£)[(c)]	Weighting[(a)]	Total cost
Carbamazepine	Modified-release tablets + tablets	1400	£174	20.0%	£35
Clobazam	Tablet	30	£137	3.9%	£5
Levetiracetam	Tablet	3000	£130	20.0%	£26
Lamotrigine	Tablet	500	£75	20.0%	£15
Perampanel	Tablet	6	£1,825	3.9%	£72
Phenytoin	Capsule	400	£299	3.9%	£12
Sodium valproate	Modified-release tablets + tablets	2000	£390	3.9%	£15
Topiramate	Tablet	450	£513	3.9%	£20
Zonisamide	Capsule	450	£213	3.9%	£8
Lacosamide	Tablet	350	£1,785	3.9%	£70
Eslicarbazepine	Tablet	1200	£1,241	3.9%	£49
Oxcarbazepine	Tablet	2100	£989	3.9%	£39
Brivaracetam	Tablet	150	£1,267	3.9%	£50
Pregabalin	Capsule	500	£50	0.3%	£0.17
Gabapentin	Capsule	3150	£130	0.3%	£0.43
				Total	**£417**

Sources:
- *(a) Committee opinion*
- *(b) Committee opinion and the British National Formulary (BNF)*[7]
- *(c) BNF*[7]*, Date accessed: 16/05/21*

1.2.7 The committee's discussion and interpretation of the evidence

No evidence was found examining the use of different criteria for referral or surgery. The committee, therefore, agreed to use the clinical and health economic evidence on the

effectiveness of surgical procedures to inform their recommendations regarding referral. The evidence and discussion are in section 1.3.

1.3 Review question: What is the effectiveness of resective surgery in epilepsy?

1.3.1 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 5: PICO characteristics of review question

Population	Inclusion: People with treatment-resistant epilepsy* Exclusion: New-born babies (under 28 days) with acute symptomatic seizures. *Epilepsy in which seizures persist defined by the ILAE as 'failure of adequate trials of 2 tolerated and appropriately chosen and used antiseizure medication schedules (whether as monotherapy or in combination) to achieve sustained seizure freedom'.
Interventions	Resective surgery: • Temporal lobectomy • Extratemporal lobectomy(parietal/frontal/occipital/ insular) Disconnective surgery: • Callosotomy • Hemispherectomy, hemispherotomy. • Temporoparietal occipital disconnection • Hypothalamic hamartoma disconnection The different surgery approaches will be pooled under an overall 'surgery' heading in the analysis.
Comparisons	Medical management / usual care / wait-list control
Outcomes	• Mortality at short-term follow-up of 12- 24 months and longer-term follow-up of >24-60 months • Seizure freedom at short-term follow-up of 12 to 24 months and longer-term follow-up of >24-60 months • Due to anticipated heterogeneity in reporting of seizure freedom, data will be extracted as presented within included studies. Where a study reports multiple variants, then all data will be extracted. For decision making priority will be given to data based on hazards (of first seizure) rather than risks or odds. • Seizure frequency (50% or greater reduction in seizure frequency) at short-term follow-up of 12 to 24 months and longer-term follow-up of >24-60 month • Quality of life (measured with a validated scale) at short-term follow-up of 12 to 24 months and longer-term follow-up of >24-60 months • Healthcare resource use • Social functioning (measures of adaptive functioning or adaptive behaviour using a validated scale) short-term follow-up of 12 to 24 months and longer-term follow-up of >24-60 months • Cognitive outcomes (including neuropsychological measures of global cognitive functioning, executive functioning and memory using a validated scale) short-term follow-up of 12 to 24 months and longer-term follow-up of >24-60 months • In children and young people: neurodevelopmental outcomes (behavioural and emotional outcomes measured with a validated scale) short-term follow-up of 12 to 24 months and longer-term follow-up of >24-60 months

	• Serious adverse events (such as infection, stroke, severe bleeding)
Study design	RCTs Systematic reviews of RCTs: For a systematic review to be included, it must be conducted to the same methodological standard as NICE guideline reviews. If sufficient details are not provided to include a relevant systematic review, the review will only be used for citation searching. Non-randomised studies will be included if there is insufficient RCT evidence (less than or equal to 2 RCTs). Non-randomised studies will be considered if they adjust for key confounders (age and gender).

1.3.2 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

For the outcome of seizure freedom, hazard ratios (HRs) for the first seizure were either not available from the papers or poorly reported. HRs were therefore calculated from Kaplan Meier survival graphs and other data provided in the studies: life tables were constructed by the reviewer, and HRs for the first seizure were calculated using excel.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.3.3 Effectiveness evidence

1.3.3.1 Included studies

A search was conducted for randomised trials comparing surgical interventions to usual care or waitlist control.

Three randomised control trials (RCTs) comprising four papers were included in the review.[18, 19, 21, 83], two RCTs were conducted in children and one in adults. These are summarised in Table 2. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

See also the study selection flow chart in Appendix C, study evidence tables in Appendix H, forest plots in 0 and GRADE tables in Appendix J.

1.3.3.2 Excluded studies

See the excluded studies list in Appendix G.

1.3.4 Summary of studies included in the effectiveness evidence

Table 6: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Dwivedi 2017[18] India	Resective surgery (n=57) Versus Medical therapy whilst waiting for surgery (n=59)	Children (median, range years) Surgery (9 years, 0.8 to 17 years) Waitlist (10 years, 2 to 17 years	At 1 year: • Mortality • Quality of life (Paediatric quality of life inventory scale) • Seizure freedom • Cognitive outcomes (Binet-Kamat scale) • Social functioning • Serious adverse events	
Engel 2012[19] USA	Resective surgery (n=15) Versus Medical therapy (n=23)	Children and young people (mean, (SD) years) Surgery (37.5 years (11.1)) Waitlist (30.9 years, (10.1))	At 2 years: • Quality of life (QOLIE-89 scale) • Seizure freedom • Seizure frequency • Cognitive outcomes (Boston Naming Test, RAVLT delayed recall) • Serious adverse events • Healthcare resource use	
Wiebe 2001[83];	Resective surgery (n=40)	Adults (mean, (SD))	At 1 year: • Mortality	

Study	Intervention and comparison	Population	Outcomes	Comments
Fiest, 2014[21] USA	Versus Medical therapy whilst waiting for surgery (n=40)	Surgery (35.5 years, (9.9)) Waitlist (34.4 years, (9.4))	• Quality of life (QOLIE-89, QOLIE-31, HUI 111, SF36 PCS, SF36 MCS) • Seizure freedom • Serious adverse events	

See Appendix H for full evidence tables.

1.3.5 Summary of the effectiveness evidence

Table 7: Clinical evidence summary: Surgery versus medical/ waitlist-control

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Waitlist-Control	Risk difference with Surgery (95% CI)
Mortality at 12-24 months	192 (2 studies) 1 year	HIGH	RD -0.01 (-0.04 to 0.02)	10 per 1000	10 fewer per 1000 (from 40 fewer to 20 more)
Quality of life - Children Paediatric QoL inventory scale. Scale from: 0 to 100.	116 (1 study) 1 year	MODERATE[1] due to risk of bias		The mean quality of life - children in the control groups was 53.9	The mean quality of life - children in the intervention groups was 22.2 points higher (16.38 to 28.02 higher)
Quality of life - Adults QOLIE-89 scale. Scale from: 0 to 100.	114 (2 studies) 1-2 years	LOW[1,2] due to risk of bias, imprecision		The mean quality of life - adults in the control groups was 64.45	The mean quality of life - adults in the intervention groups was 9.67 points higher (5.27 to 14.08 higher)
Quality of life (change score) QOLIE-89 cognitive scale. Scale from: 0 to 100.	38 (1 study) 2 years	VERY LOW[1,2] due to risk of bias, imprecision		The mean quality of life (change score) in the control groups was 0.1	The mean quality of life (change score) in the intervention groups was 7.7 higher (1.03 to 14.37 higher)
Quality of life. QOLIE-89; Adjusted odds of achieving clinically significant improvement in QOLIE-89 (10.1 points) over 1 year period	76 (1 study) 1 year	MODERATE[1] due to risk of bias	Adjusted OR: 15.1 (95% CI 2.7-84.8)	Not available	RD not calculable
Quality of life. QOLIE-31; Adjusted odds of achieving clinically significant improvement in QOLIE-31 (11.8	76 (1 study) 1 year	MODERATE[1] due to risk of bias	Adjusted OR: 15.2 (95% CI 2.6-88.0)	Not available	RD not calculable

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Waitlist-Control	Risk difference with Surgery (95% CI)
points) over 1 year period					
Quality of life. HUI-111; Adjusted odds of achieving clinically significant improvement in HUI 111 (0.2 points) over 1 year period	76 (1 study) 1 year	MODERATE[1] due to risk of bias	Adjusted OR: 6.0 (95% CI 1.7-21.5)	Not available	RD not calculable
Quality of life. SF-36 PCS; Adjusted odds of achieving clinically significant improvement in SF-36 PCS (4.6 point) over 1 year period	76 (1 study) 1 year	LOW[1,2] due to risk of bias, imprecision	Adjusted OR: 2.4 (95% CI 1.0-5.8)	Not available	RD not calculable
Quality of life. SF-36 MCS; Adjusted odds of achieving clinically significant improvement in SF-36 MCS (3.0 points) over 1 year period	76 (1 study) 1 year	LOW[1,2] due to risk of bias, imprecision	Adjusted OR: 2.5 (95% CI 1.0-6.6)	Not available	RD not calculable
Seizure freedom: Hazard of first seizure*	230 (3 studies) 1 years	HIGH	HR 0.29 (0.21 to 0.39)	Not available	RD not calculable
Seizure freedom in second year of follow up	38 (1 study) 2 years	MODERATE[1] due to risk of bias	Peto OR 32.19 (7.82 to 132.54)	0 per 1000	730 more per 1000 (from 510 more to 960 more)
Seizure frequency at 22 to 24 months	32 (1 study) 2 years	LOW[1,2] due to risk of bias, imprecision		The mean seizure frequency in the control groups was 9.47	The mean seizure frequency in the intervention groups at 22 to 24 months was 9.16 lower (19.1 lower to 0.78 higher)
Cognitive outcomes Binet-Kamat test	116 (1 study) 1 year	HIGH		The mean cognitive outcomes in the control groups was 58.9	The mean cognitive outcomes in the intervention groups was 3.8 higher (3.61 lower to 11.21 higher)
Cognitive outcomes (change score) Boston Naming Test	38 (1 study) 2 years	LOW[1,2] due to risk of bias, imprecision		The mean cognitive outcomes (change score) in the control	The mean cognitive outcomes (change score) in the intervention groups was 4.2 lower

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Waitlist-Control	Risk difference with Surgery (95% CI)
				groups was 0.8	(8.43 lower to 0.03 higher)
Cognitive outcomes (change score) RAVLT delayed recall	38 (1 study) 2 years	LOW[1,2] due to risk of bias, imprecision		The mean cognitive outcomes (change score) in the control groups was 0.6	The mean cognitive outcomes (change score) in the intervention groups was 2.1 lower (4.1 to 0.1 lower)
Social functioning Child behaviour Checklist. Scale from: 0 to 100.	116 (1 study) 1 year	MODERATE[1] due to risk of bias		The mean social functioning in the control groups was 68.6	The mean social functioning in the intervention groups was 11.4 lower (14.01 to 8.79 lower)
Serious adverse events	230 (3 studies) 1-2 years	MODERATE[1] due to risk of bias	Peto OR RR 7.30 (3.41 to 15.61)	33 per 1000	230 more per 1000 (from 140 more to 320 more)
Number of AEDs used	38 (1 study) 2 years	LOW[1,2] due to risk of bias, imprecision		The mean number of AEDs used in the control groups was 1.8	The mean number of AEDs used in the intervention groups was 0.30 lower (0.84 lower to 0.24 higher)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
*Hazard is for first seizure, so a lower hazard represents a benefit; thus, a HR <1 indicates a benefit for surgery

See Appendix J for full GRADE tables.

1.3.6 Economic evidence

1.3.6.1 Included studies

Two health economic studies in adults, with the relevant comparison, were included in this review. [10,23,29]

These studies both focused on the cost-effectiveness of diagnostic strategies to localise the epileptogenic zone prior to surgery rather than the cost-effectiveness of surgery itself. This pre-surgery assessment is costly. Not everyone who has these tests will then go on to have the surgery, but these costs need to be considered as part of the surgery because they will determine who eventually receives surgery and the overall cost per surgery candidate (e.g., if you have to test 10 people to find one candidate or alternatively test 100 to find one candidate then this affects the costs per surgery). Additionally, the benefit of a diagnostic test comes from the intervention that can follow, rather than the test itself, and therefore as some people will receive surgery in the diagnostic strategy arms (dependent on the results of the test), then the outcomes of those strategies are still relevant for this surgery question. It is possible to compare the cost-effectiveness of surgery with no surgery from such studies, as long as they have a medical management arm and the diagnostic pathway is relevant.

These data are summarised in the health economic evidence profiles below (**Table 8** and **Table 9**) and the health economic evidence tables in Appendix E.

1.3.7 Excluded studies

Four economic studies [9, 44, 50, 82, 12]relating to this review question were identified but were excluded due to methodological limitations and the availability of more applicable evidence. These are listed in Appendix G, with reasons for exclusion given.

See also the health economic study selection flow chart in Appendix D.

1.3.8 Summary of included economic evidence

Table 8: Health economic evidence profile: Testing strategies following discordant EEG and MRI findings versus medical management

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Burch 2012 [10] & Hinde 2014 [23](United Kingdom)	Partially applicable [(a)]	Minor limitations [(b)]	• Probabilistic decision analytic model. Decision tree followed by Markov model. • Cost-utility analysis (QALYs) • Population: Medically refractory epileptic patients with TLE who have had discordant findings from initial video-EEG and MRI scans. • Comparators: 1) Medical Management (MM) 2) FDG-PET. If positive result offered surgery, if negative or uncertain offered MM 3) FDG-PET. If positive result, offered surgery, if negative, MM, if uncertain, iEEG (if positive, offered surgery, otherwise MM) Time horizon: lifetime	(2-1) £2,845 (3-1)[(c)] £3,927	(2-1) 1.71 QALYs (3-1)[(c)] 2.04	**Intervention 2 vs. 1:** £1,671 per QALY gained **Intervention 3 vs. 1:** [(c)] £1,925 per QALY gained	Probability Intervention 1 cost effective (£20/£30K threshold): 14%/13% Probability Intervention 2 cost effective (£20/£30K threshold): 3%/3% MM and surgery outcomes equivalent after 1 year - both strategies remained cost effective (ICER 2 = £11,536; ICER 3[(c)] = £13,794). PSA indicated that the disutility of Disabling Seizure for MM and surgery (no complications) had the potential to alter results; but strategy 3 was still the most cost effective in the majority of cases (0.85 and 0.93, respectively) The results became more sensitive to the short-term effectiveness of surgery, whereby if the success rate of surgery is < 55% then

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
							Strategy 1 would be most cost effective. Conclusion from base case and the scenario analysis would change if compliance to surgery was < 20%.

Abbreviations DS= disabling seizure; EEG= electroencephalography; FDG-PET= fluorodeoxyglucose positron emission tomography; ICER= incremental cost-effectiveness ratio; iEEG= invasive/intracranial electroencephalography; MM= medical management; MRI= magnetic resonance imaging; PSA= probabilistic sensitivity analysis; QALY= quality-adjusted life years; TLE= temporal lobe epilepsy

(a) Study evaluates the cost effectiveness of different diagnostic strategies for potential patients undergoing TLE surgery. The diagnostic testing strategies used to identify eligible patients may not reflect those used in current practice.

(b) Some simplifying assumptions are made due to lack of evidence available. In some instances, it is not apparent what timeframe is being analysed in evidence drawn from the wider literature used to inform model parameters. Treatment effects based on a mix of RCTs and observational data

(c) Calculated from paper. The paper compares strategy 3 vs. 2 but we are interested in 3 vs. 1 so we can compare the different diagnostic strategies to medical management.

Table 9: Health economic evidence profile: Intracranial EEG (subdural grid electrodes) versus iEEG (stereoelectroencephalography) versus medical management

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Kovacs 2021[29] (Hungary)	Partially applicable [(a)]	Minor limitations [(b)]	• Probabilistic decision analytic model. Decision tree followed by Markov model. • Cost-utility analysis (QALYs) • Population: Adults with drug-resistant, partial-onset epilepsy. • Comparators: 1) Medical Management (MM)	(2-1) £9,647 (3-1)[(c)] £16,837	(2-1) 3.444 QALYs (3-1)[(c)] 3.931	**Intervention 2 vs. 1:** £2,802 per QALY gained **Intervention 3 vs. 1:** £4,284 per QALY gained	Probability Intervention 2 cost effective (£38K threshold): 99.7% Probability Intervention 3 cost effective (£38K threshold): 99.5% One-way sensitivity and scenario analyses undertaken. None of these deterministic sensitivity analyses lead to a substantial change in ICER

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			2) intracranial EEG (iEEG) monitoring: placement of subdural grid electrodes (SDGs) 3) iEEG: stereotactic implantation of depth electrodes (stereoelectroencephalography or SEEG). After either iEEG, if successful epileptogenic zone localisation they are offered surgery (temporal or extratemporal resective surgery). If unsuccessful offered MM. Time horizon: 30 years				or resulted in an ICER over £38K.

Abbreviations DS= disabling seizure; ICER= incremental cost-effectiveness ratio; iEEG= invasive/intracranial electroencephalography; MM= medical management; PSA= probabilistic sensitivity analysis; QALY= quality-adjusted life years; SDGs= subdural grid electrodes; SEEG= stereoelectroencephalography

(a) Study evaluates the cost effectiveness of different diagnostic strategies for potential patients undergoing temporal or extratemporal resective surgery. The diagnostic testing strategies used to identify eligible patients may not reflect those used in current practice. Non-UK perspective may not reflect current UK NHS practice. EQ-5D not used for QoL.

(b) Unclear if literature used to inform model parameters were appropriate for this subset of patients who would undergo iEEG diagnostic procedures prior to surgery. Treatment effects based on a mix of RCTs and observational data. Not all data sources clearly reported.

1.3.9 Economic model

An original cost-utility analysis was developed, assessing the cost-effectiveness of resective epilepsy surgery in adults with drug refectory epilepsy. Original health economic modelling was also planned to model the cost-effectiveness of resective epilepsy surgery in children, but insufficient data were available to model for this population. Full details of the health economic analysis can be found in the Economic analysis report.

The committee identified this as a high priority area as they thought that currently, there could be a reluctance to refer people for resective epilepsy surgery. The committee wanted to evaluate the benefits of resective epilepsy in terms of improved seizure freedom and long-term cost savings.

Model structure

The following comparators were included in the analysis:

1. Resective epilepsy surgery
2. Medical management

The population of the analysis was adults with drug refractory epilepsy.

A two-part model was developed, which included a decision tree to model post-procedural outcomes (over 1 year) followed by a Markov model for the estimation of quality-adjusted life-years and costs over the lifetime of the patient. The decision tree structure can be found in Figure 1, and long-term Markov model structure can be found in Figure 2.

Figure 1: Decision tree

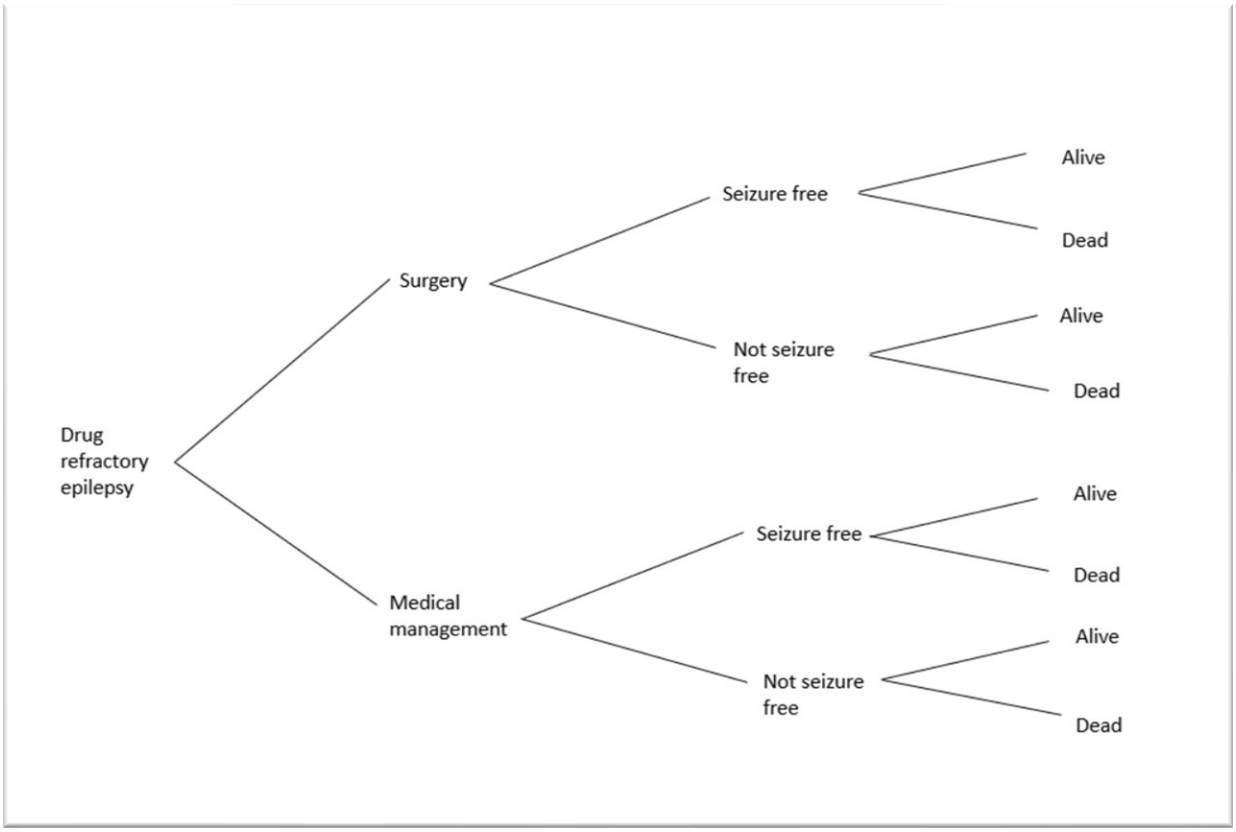
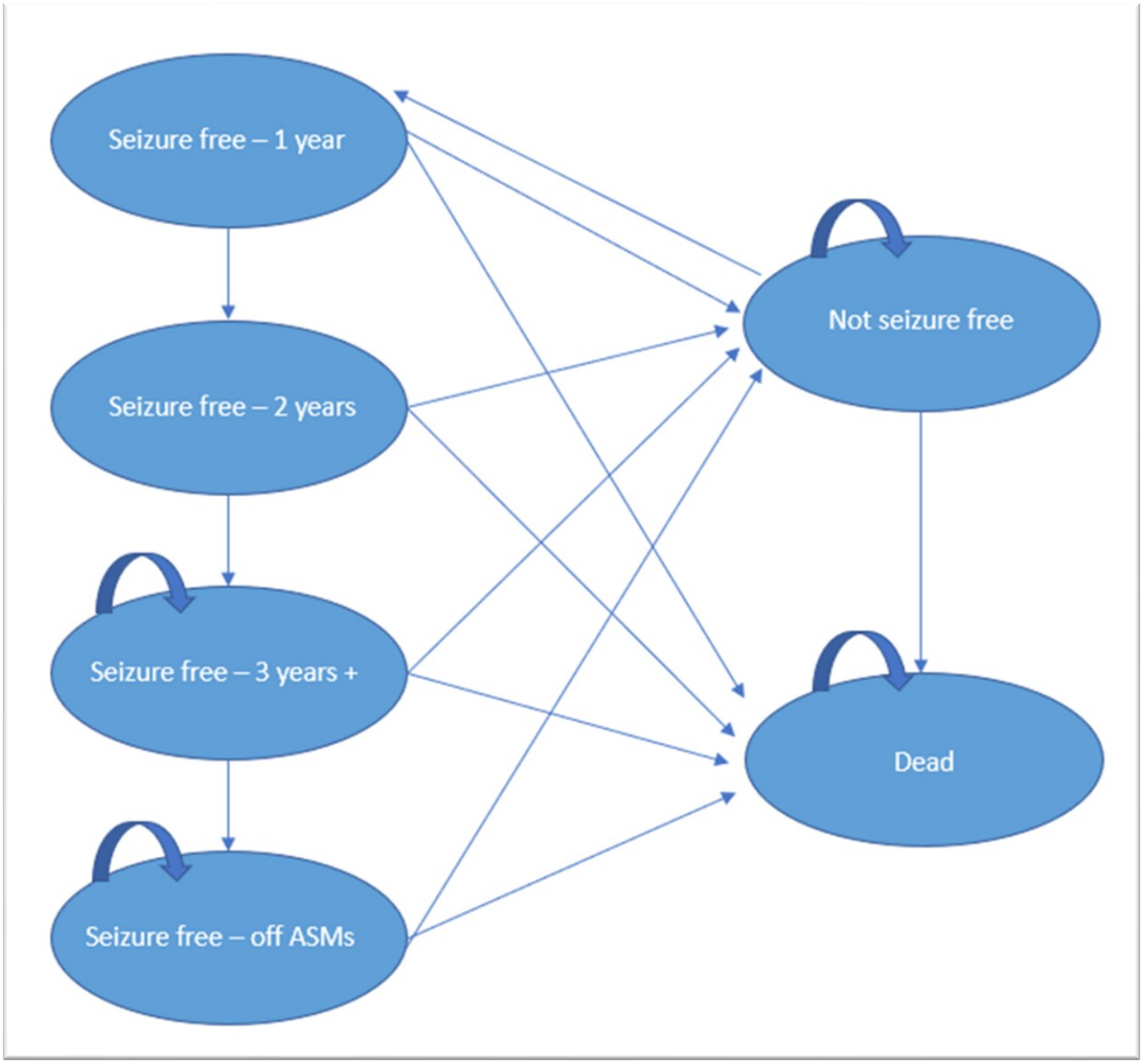


Figure 2: Markov model



The model base case analysis was built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run repeatedly – 5,000 times - and results were summarised.

Data inputs

- Seizure freedom at one year was taken from the two trials in adults in the guideline clinical review[19, 83]
- Longer-term outcomes from surgery were taken from de Tisi 2011[16]
- Longer-term outcomes for medical management were taken from Callaghan 2011[11]
- Standardised mortality ratios[58 67 2, 36, 43] were applied to national life tables for England[46]. These were differentiated by seizure-free and not seizure-free
- Utilities came from the SANAD study[77]
- Some costs were included only in the surgery arm:
    - The surgical procedure including hospital stay

    - Preoperative assessment
    - Treatment of long-term complications arising from surgery
    - Re-operation
- Other costs were attributed to both the surgery and medical management arms but were determined by whether the patient was in a state of seizure-freedom or disabling seizures:
    - Anti-seizure medication
    - GP and outpatient hospital visits
    - Inpatient stays
- The impact of surgical complications was based on expert and committee opinion. The risk of long-term complications was 4%. For patients that experienced a complication, there was a reduction in EQ-5D of 0.2, and an additional cost per year of £5,000 was applied over the lifetime.
- Reoperation was 4% based on committee opinion
- Resource use involved with preoperative assessment came from a bespoke survey of adult surgical centres (see Table 10)
- The impact of seizure freedom on resource use was based on Jacoby 1998[25], Wieser [86] and expert opinion
- The unit costs of surgery, tests, appointments, admissions, and drugs came from standard NHS sources [42 7]

Assessment for resective surgery survey

A comprehensive survey was administered to participating adult epilepsy surgery centres to obtain the average number of tests for people undergoing assessment for resective epilepsy surgery. Ten surgical centres submitted data for a total of 762 people.

Overall, fourteen epilepsy surgical centres were contacted, resulting in a response rate of 71%. The committee was provided with a list of the participating surgical centres and concluded the data would provide a representative sample to obtain the resource use for preoperative assessment.

The mean number of tests are reported in Table 10.

Table 10: Preoperative assessment cost

Test	Mean number of tests (n=762)	Unit cost	Mean cost per patient investigated
History & Examination	1.4	£217	£315
Neuropsychology assessment	0.9	£334	£291
Neuropsychiatry assessment	0.5	£346	£157
Magnetic resonance imaging (MRI)	1.6	£146	£234
Initial videotelemetry	0.9	£2,791	£2,630
Repeat videotelemetry	0.3	£2,791	£736
Positron emission tomography (PET)	0.4	£666	£270
Occupational therapy	0.0052	£111	£0.58
Physiotherapy	0.0052	£59	£0.31
Stereoelectroencephalography (sEEG)	0.2	£14,638	£2,497
Single-photon emission computed tomography (SPECT)	0.1	£342	£31
Functional magnetic resonance imaging (fMRI)	0.4	£146[(a)]	£55
Amytal testing	0.0354	£3,545[(b)]	£126
Magnetoencephalography (MEG)	0.0197	£3,250[(c)]	£64

Test	Mean number of tests (n=762)	Unit cost	Mean cost per patient investigated
Multidisciplinary team meeting	1.6	£226	£362
Pre-surgical counselling	0.7	£346	£235
Informed consent assessment	0.4	£224	£83
Electrocochleography (ECoG)	0.0236	£4,000[(d)]	£94
Total cost			**£8,182**

The centres were also asked about the outcome of patients being assessed for surgery to assess what proportion of those being assessed for surgery proceeds to have a surgical resection. The probability of being a surgery candidate was determined to be 41.3% across all centres. In the model, we add the test of costing those patients that did not go on to have surgery as well as the cost of the surgical patient themselves. So, the total assessment cost per patient undergoing surgery was £8,182 + £11,628 = £19,809, where £11,628=£81,812*(58.7%)/41.3%.

Cost-effectiveness Results

The base case probabilistic model results indicated surgery was cost-effective at NICE's £20,000 threshold with a cost per QALY of £11,425. The total cost for surgery was higher compared to medical management (£56,204 compared to £31,627), but the total QALYs were also higher for surgery (15.91 compared to 13.76). The higher cost for surgery was largely driven by the high cost of assessment for resective epilepsy surgery and procedure costs. Greater QALYs for surgery were obtained because more people receiving resective epilepsy surgery achieve seizure freedom compared to those receiving medical management, and higher standardised mortality ratios are associated with people who are not seizure-free.

Table 11: Base case cost effectiveness results (probabilistic)

Year	Surgery	Medical management	Surgery minus Medical management
Mean costs	£56,204	£31,627	£24,577
Mean QALYs	15.91	13.76	2.15
Incremental cost per QALY gained	-	-	£11,425
Probability cost-effective at £20,000 per QALY	96.5%	3.5%	
Probability cost-effective at 30,000 per QALY	99.3%	0.7%	

The sensitivity analyses showed that the results were a little sensitive to the utility values, and costs, but only when the time horizon was lowered (to 15 years) did the cost per QALY gained exceed the £20,000 per QALY gained threshold - Table 12. Only when all the most pessimistic assumptions were made did the cost per QALY gained exceed £30,000 per QALY gained.

Table 12: Sensitivity analysis (deterministic)

Scenario	Incremental costs	Incremental QALYs	Incremental cost per QALY gained
Determinist base case	£23,601	2.13	£11,069

Scenario	Incremental costs	Incremental QALYs	Incremental cost per QALY gained
Probabilistic base case	£24,577	2.15	£11,425
Utilities assuming 50% of people in the surgery arm have a ≥50% reduction in seizures	£23,601	2.30	£10,277
Utilities from Kovacs 2021	£23,601	3.03	£7,780
Utilities from the previous NICE guidance	£23,601	1.32	£17,821
The probability of receiving surgery is higher	£17,427	2.13	£8,174
The probability of receiving surgery is lower	£35,259	2.13	£16,537
Treatment effect from Wiebe 2001 only	£23,731	2.10	£11,314
SMR for seizure free is 1.11	£23,724	2.34	£10,158
Surgery relapse rate higher	£24,601	1.95	£12,608
Surgery relapse rate lower	£22,472	2.33	£9,630
Assessment for resective surgery costs higher	£35,878	2.13	£16,827
Assessment for resective surgery costs lower	£16,948	2.13	£7,949
Surgery costs higher	£29,783	2.13	£13,969
Surgery costs lower	£21,726	2.13	£10,190
Time horizon 15 years	£26,979	0.96	£28,231
No discontinuation of anti-seizure medications	£29,852	2.13	£14,001
Higher cost for sEEG	£27,783	2.13	£13,031
Overall best case	£9,931	3.53	£2,811
Overall worst case	£66,725	0.37	£182,331

1.3.10 Unit costs

Please see unit cost presented in section 1.2.6.

1.3.11 Evidence statements

Economic

- One cost-utility analysis found that fluorodeoxyglucose positron emission tomography and fluorodeoxyglucose positron emission tomography plus intracranial electroencephalography were cost-effective compared to medical management (ICER: £1,671 per QALY gained and £1,925 per QALY gained respectively). This study was assessed as partially applicable with minor limitations (Burch 2012).
- One cost-utility analysis found that subdural grid electrodes and stereoelectroencephalography were cost-effective compared to medical management (ICER: £2,802 per QALY gained and £4,284 per QALY gained respectively). This study was assessed as partially applicable with minor limitations (Kovacs 2021).
- One original cost-utility analysis found that resective epilepsy surgery in adults is cost effective compared to medical management for treating drug-refractory epilepsy (ICER:

£11,425 per QALY gained). This study was assessed as directly applicable with minor limitations.

1.4 The committee's discussion and interpretation of the evidence

1.4.1 The outcomes that matter most

The most important outcome was agreed by the committee to be quality of life, as this encapsulates the effects of treatment most relevant to the person with epilepsy. Other outcomes of similar importance were mortality, seizure recurrence, serious adverse events and cognition. Mortality and seizure recurrence were regarded as highly relevant outcomes to evaluate the potential harms of not using surgery, whilst serious adverse events and cognition were deemed the outcomes best suited to measure the harms of surgery itself. Although serious adverse events and cognition had originally been deemed non-critical outcomes at the protocol stage, it became apparent during discussion of the evidence that these were centrally important to decisions concerning recommendation of surgical intervention, because they could have a significant impact on function. All other outcomes were deemed important but less liable to affect recommendation decisions.

1.4.2 The quality of the evidence

The evidence included for this review was for resective surgery only. Quality of the evidence ranged from 'high' to 'very low'. The most common reasons for downgrading of ratings were imprecision and risk of bias. The committee noted that imprecision was related to a lack of power in the included studies, which had relatively small sample sizes. The risk of bias was usually related to a lack of blinding (2 studies) or lack of allocation concealment (1 study). Given the nature of the interventions, surgery versus waiting list control, lack of blinding was inevitable. Therefore, the committee agreed that despite the risk of bias ratings, the studies were well conducted, and the overall quality was good. The committee was relatively confident of the validity of the evidence and supported a strong recommendation for surgery in both adults and children.

1.4.3 Benefits and harms

The committee agreed that surgery led to much better improvements in quality of life than medical care and that this was a crucial benefit of surgery for both children and adults with drug=resistant epilepsy. This benefit was generally of large magnitude, suggesting an effect that would be noticeable and important to the person with epilepsy, and it was also highly unlikely to be due to chance (sampling error). The committee also agreed that the greater reductions in seizure recurrence resulting from surgery would be an important benefit to the patient, particularly in view of the large effect size observed from the time to event data. Although surgery's relative effects on mortality were small and consistent with possible sampling error, the committee stated that the single death occurring in the medical care group was made more significant by virtue of it being: sudden and unexpected. This suggested it might be due to SUDEP, which was viewed by the committee as potential harm resulting from *not* providing surgery in a timely fashion.

The committee also weighed up the accompanying harms of surgery in terms of clear examples of greater cognitive deficits post-surgery in the studies. The committee questioned whether pre-surgical methods such as the sodium amobarbital procedure (Wada test) had been carried out in the studies to try to reduce the likelihood of these harmful effects occurring. The fact that these methods had not been used in the included studies suggested that the reported cognitive defects might not always be an inevitable result of surgery, as

they might, in practice, be ameliorated to some extent by suitable pre-surgical assessment strategies.

The cognitive tests showing harms for surgery were discussed further in some detail by the committee. In relation to the 'Boston Naming Test', members of the committee explained how patients often find that deficits in this test do not always translate to dysfunction in everyday life, and that the majority of patients would accept living with a reduction in naming capacity. Furthermore, it was discussed how there are approaches that may be used to minimise any disability caused by naming difficulties. These might include standard interventions offered by speech and language therapists and neuropsychologists, such as phonologic and orthographic cues, semantic feature analysis, contingency-based cueing hierarchies, and repeated conversational engagement. With respect to the 'delayed recall test', the committee accepted that the reported deficits were a more intractable problem, as there were few ways of avoiding them. It was described how such deficits are manifested in about a third of cases by a cognitive 'aging' of around 10 years. However, the committee stressed that the risks of cognitive decline when *having* surgery were comparable to the risk of SUDEP when *not* having surgery. Given that cognitive decline is less serious than death, the committee agreed that the benefits of surgery were not negated by the evidence of cognitive decline.

The other serious adverse events observed in the studies, such as motor deficits, were also discussed, but the consensus was that these largely self-limiting effects did not shift the overall balance of benefits and harms away from an overall benefit for surgery. The committee acknowledged the importance of counselling as part of a surgical workup to discuss the balance between risks and benefits of surgery with patients or their carers to enable informed decision making.

The committee also discussed how the balance of benefits and risks depends on the complexity of the surgery, with more complex surgery leading to less benefits and more risks. In relation to this, the committee discussed how paediatric epilepsy surgery was very often more complex than adult surgery. For example, paediatric surgery would often involve more extratemporal surgery, as well as potentially risky procedures such as hemispherotomy or corpus callosotomy. However, it was agreed that even in very complex paediatric surgery the balance of benefits and harm from surgery would often still be superior to that of medical care.

The committee noted that no evidence had been found for surgery in people with learning disabilities and discussed that this population are less likely to have surgery. This may happen because of difficulties in gaining consent, or they are not referred due to a belief they would be unable to cope with the surgical assessment. In addition, the committee referred to evidence that this group might have poorer outcomes from surgery because of intractable brain pathology. The committee also noted people with genetic abnormalities may also sometimes be excluded from referral for a surgical assessment, and agreed that people with learning disabilities and those with genetic abnormalities should be considered for surgical assessment when it is indicated.

The committee agreed that any referral for surgery should be made as soon as a person had been identified as appropriate for surgery. It was agreed that early referral would avoid unnecessary risks resulting from further seizures during a waiting period, without any attendant benefits from such a delay. The committee discussed the reasons why delays tend to occur before referrals are made, even when a patient is clearly suitable for surgery. General misunderstanding of what surgery can offer was offered as a major reason, and it was discussed how improved education of clinicians was important.

The committee was therefore unanimous that the overall clinical benefits of surgery should make it an option for everyone – both adults and children - with drug-resistant epilepsy i.e., has tried two or more ASMs and is experiencing at least 2 seizures a month. The need to make decisions based on the individual patient's characteristics and wishes was stressed,

but it was also discussed how all patients with drug-resistant epilepsy should be given an opportunity to be referred to a tertiary centre that could consider a surgical strategy for the patient. The committee agreed that an adult with drug-resistant epilepsy should be referred to a specialist tertiary centre, and a child should be referred to a tertiary paediatric neurology service, both for consideration of surgical treatment, as early as possible.

1.4.4 Cost effectiveness and resource use

Two economic evaluations were identified for the review question assessing the cost-effectiveness of resective epilepsy surgery (Burch 2012 & Kovacs 2021). No economic evaluations were identified for the review question assessing the criteria for assessment for resective epilepsy surgery.

Burch 2012 assessed the cost effectiveness of testing strategies for assessment for resective epilepsy surgery following discordant EEG and MRI findings from a UK NHS and personal social services perspective. They compared three strategies:

1. Medical management (MM)
2. Patients received FDG-PET.
    a. if the results of the preoperative assessment test were positive (e.g., the epileptic zone was located, and resective epilepsy surgery was feasible), patients received surgery.
    b. If the results of the FDG-PET were negative or uncertain, patients received MM.
3. Patients first received FDG-PET.
    a. Then, as in intervention 2, if the results were positive, patients received surgery,
    b. if the results were negative, patients received MM.
    c. where the results of the test were uncertain patients received an iEEG.
        i. A positive iEEG resulted in surgery being undertaken and
        ii. a negative or uncertain result led to continued treatment with MM.

For FDG-PET compared to MM the cost was £1,671 per QALY gained, and for FDG-PET +iEEG compared to MM, it was £1,925 per QALY gained.

Kovacs 2021 also assessed the cost-effectiveness of three different strategies from a Hungarian health care perspective. The cost-utility analysis undertaken by Kovacs 2021 was based on the cost-effectiveness analysis undertaken by Burch 2012, with differences in some of the data inputs used to populate the model and the preoperative assessment tests being evaluated. In Kovacs 2021. MM was compared to two different types of iEEG monitoring – placement of subdural grid electrodes (SDG) and stereotactic implantation of depth electrodes (SEEG). If localisation of the epileptic zone was identified, resective epilepsy surgery would be conducted. However, if the iEEG was unsuccessful in identifying the epileptic zone patients would receive MM. SDG cost an extra £2,802 compared to MM and SEEG cost £4,284 per QALY gained compared to MM.

Neither of these economic evaluations captured the RCT evidence identified in the clinical review. In addition, the committee noted that some of the data inputs used in these studies might not reflect the majority of epilepsy surgery patients. The target population in these studies would typically be people where the epileptic zone is more difficult to localise as the preoperative assessment tests being evaluated would normally be conducted at the latter stages of the assessment for resective epilepsy surgery pathway. The committee acknowledged that when the epileptic zone is more difficult to localise – and subsequently the area of the brain to resect may not be as well defined – poorer outcomes post-surgery may be observed compared to people where the epileptic zone was identified through fewer preoperative assessment tests.

The health economic studies included in the review were limited to the cost-effectiveness of specific preoperative assessment tests; therefore, the costs of other preoperative assessment tests were not included in the overall assessment of the cost effectiveness.

Due to the high clinical and economic importance concerning the cost effectiveness of resective epilepsy surgery original health economic modelling was also undertaken to assess the cost effectiveness of resective epilepsy surgery in adults. Unfortunately, there was insufficient data to model the cost-effectiveness of resective epilepsy surgery in children. The lifetime cost of surgery was higher than for MM (£56,204 and £31,627 respectively) but the QALYs gained were also greater in the surgery arm (15.91 QALYs compared to 13.76 QALYs). Compared with medical management, surgery cost an extra £11,425 per QALY gained, which is below NICE's £20,000 threshold.

The clinical evidence included in the review was included in our original health economic analysis; however, it only provided data to populate the data in our 1-year decision tree. This is because it is challenging to conduct long-term RCTs assessing the effectiveness of epilepsy surgery due to cross-over. Observational data was therefore required to inform the long-term effectiveness of surgery and MM. A large long-term observational study based on a UK population (de Tisi 2011) was used to populate the long-term effectiveness outcomes for people after epilepsy surgery. However, there were fewer data available for a drug refractory population who continue MM. These data were subsequently taken from Callaghan 2011, which evaluated the remission and relapse rate in a drug-resistant epilepsy cohort of 246 patients from the USA. In de Tisi 2011, data were reported up to 15 years and in Callaghan 2011 data were reported up to 5 years. To account for the potential uncertainties in the long-term (lifetime) data for both surgery and medical management, a sensitivity analysis was conducted using a 15-year time horizon. Although, at 15 years, there is still uncertainty over medical management because data in Callaghan 2011, was limited to 5-year follow-up. In this analysis, the cost per QALY gained was £28,231, which is above NICE's £20,000 threshold but below NICE's £30,000 threshold. However, the committee thought that this was conservative, and it is reasonable to assume that the impact of surgery can continue for longer than 15 years for most individuals.

In most long-term outcome studies (including de Tisi 2011) assessing epilepsy surgery, seizure freedom was defined as being completely seizure-free or with only simple partial seizures, now termed focal-aware seizures (FAS). This is reasonable but this definition did not correspond with the definition used in the trials or the studies that were sourced for health state utility scores and standardised mortality ratios, which were only people who were completely seizure-free. To overcome the challenges posed by these differential definitions, adjustments were made to the standardised mortality ratios (SMRs) and utilities for seizure freedom in the surgery arm using the proportion of people that experienced FAS in de Tisi 2011. The utility and mortality for people experiencing only FAS is not known, and so conservative assumptions were made, which if anything, might have under-estimated the benefits of surgery, but as only 18% of people of the seizure-free sample had experienced FAS, the committee concluded this would not alter the overall results of the cost-effectiveness analysis.

Callaghan 2011's definition of drug refractory epilepsy was stricter than the current definition of drug refractory. Callaghan defined drug-resistant epilepsy as people who had failed on at least two antiseizure medications (ASMs) and were experiencing at least one seizure per month. The current ILAE definition of drug refractory epilepsy is the occurrence of uncontrolled seizures despite two tolerated and appropriately chosen ASMs. Therefore, the cohort of people in Callaghan 2011 may have had more severe drug refectory epilepsy compared to a drug-resistant cohort as defined by the ILAE definition. The committee did, however, note that the estimated proportion of people entering seizure freedom (5.6%) and relapsing (22%) each year seemed reasonable.

The committee discussed how the results of the adult epilepsy model may translate into a paediatric population. The committee discussed that the cost of pre-surgical evaluation may be more expensive for children as they might require additional tests. However, the committee noted seizure freedom after resective epilepsy surgery might be more likely in children than adults, and the benefits for children could be accrued over a longer period.[33, 34]

There is also some evidence that if seizure-free they are more likely to be able to stop taking anti-seizure medication,[33, 34] which would be cost-saving in the longer term. In addition, the committee noted children with drug refractory epilepsy are likely to have more outpatient appointments than adults. Therefore, rendering children seizure could result in additional downstream cost savings because less outpatient appointments are required for people rendered seizure-free. Additional studies have shown children with drug refractory epilepsy who receive surgery have, better cognitive development, better outcomes in school, and greater chances of employment in adult life compared to those who continue to receive MM.[8, 64-66]

A lifetime re-operation rate of 4% was incorporated in the adult, model and the committee concluded this rate of 4% would likely be similar in a paediatric population. The committee did, however, note that for children undergoing resective epilepsy surgery, the need for re-operation may also arise in adulthood which would incur additional costs however, this is only for a small proportion of people. The committee concluded that the cost savings observed in a paediatric population would likely outweigh the additional costs that may be incurred from preoperative assessment and additional re-operation in adulthood and therefore concluded resective epilepsy surgery in children is highly likely to be cost-effective.

Overall, based on the results of the included health economic studies and the original health economic analysis, the committee concluded that resective epilepsy surgery in a drug refractory population is highly likely to be cost-effective in both adults and children. The committee discussed that although there are limitations with the evidence used in the health economic model, these were dealt with in the most appropriate way.

In current practice, epilepsies services for surgery are managed separately for adults and children. Epilepsy services for children are run by the Children's Epilepsy Surgery Service (CESS), whereas epilepsy surgery for adults is managed at tertiary epilepsy centres. The CESS centres were developed to increase the levels of paediatric resective epilepsy surgery in England. Since CESS was developed, the number of children undergoing preoperative assessment and resective epilepsy surgery in children has increased. The committee noted that the target number of referrals for preoperative assessment set by CESS, are currently below target. Target levels for preoperative assessment and resective epilepsy surgery are predicted by CESS epidemiologically. The committee concluded the recommendations made would help CESS achieve their targets and therefore are not expected to result in a substantial resource impact.

Resective epilepsy surgery is provided for adults at tertiary epilepsy centres. However, the committee noted that levels of referral for epilepsy surgery are sub-optimal. The committee prioritised this area for original health economic modelling in the hope they could recommend everyone with drug refractory epilepsy be referred for pre-surgical evaluation.

The health economic model incorporated the cost of pre-surgical evaluation in the total costs of surgery (including the costs for people who were referred for surgery and underwent pre-surgical evaluation but did not go on to have surgery). Sensitivity analyses were also conducted, assuming a higher and lower cost for assessment for resective epilepsy surgery. This was calculated at the highest cost out of the nine participating centres and the lowest cost. When the higher cost was used, resective epilepsy was still cost-effective (£16,827 per QALY gained). The committee noted that this cost for assessment of resective epilepsy (£13,178) is likely more reflective of being undergoing more complex preoperative assessments.

Overall, as surgery was assessed to be cost effective the committee concluded they were able to make a strong recommendation to refer adults, children and young people with drug resistant epilepsy for assessment for resective surgery.

The committee noted that in current practice referral to an epilepsy surgery centre for people who are drug refractory can take years. This is due to several factors, such as the misconception of clinical uncertainty surrounding the efficacy of surgery or healthcare professionals taking a view that referral should be a 'last resort' once a large number of ASMs have been tried. The committee discussed that once a person has failed two appropriately chosen ASMs the chances of obtaining seizure freedom through use of ASMs diminishes significantly. The committee noted that referral to an epilepsy surgery centre to enter the assessment for resective epilepsy surgery pathway does not necessarily mean surgery will take place for the patient in question. A person may not be an eligible candidate for epilepsy surgery, or they may not wish to proceed with surgery. Given all of the data presented, the committee was, though, clear that people with drug-resistant epilepsy should be referred promptly to a tertiary epilepsy centre for consideration of epilepsy surgery.

This recommendation may lead to a substantial resource impact as more adults will likely be referred for assessment for resective epilepsy surgery. The degree of the impact will be dependent on how many people decide to undergo assessment for resective epilepsy once referred because the assessment for resective epilepsy surgery is resource intensive. The committee noted that even if more people are referred for assessment for resective epilepsy the proportion of people who are eligible for surgery and proceed to resective epilepsy surgery is unlikely to change substantially.

1.4.5 Other factors the committee took into account

The committee noted that the evidence was only in people who were already drug-resistant, and that the comparator in these studies was medical management. This initially suggests a certain bias in the studies over and above that evaluated in the risk of bias assessments, resulting from the samples being made up of people who would be predisposed to do badly on the comparator treatment. This would naturally increase the likelihood for the intervention to appear superior. However, it was also realised that there are only two established ways to treat epilepsy – drugs or surgery. If the drugs work well, then surgery would probably not be contemplated, but if the drugs are ineffective, then surgery is a viable option. Hence it is correct that surgery should be tested for efficacy in the population where the drugs don't achieve their aim.

1.4.6 Recommendations supported by this evidence review

This evidence review supports recommendations 8.2.1 – 8.2.4 .

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Appendices

Appendix A Review protocols

A.1 Review protocol for surgery referral criteria

ID	Field	Content
1.	Review title	What are the criteria for referral to epilepsy surgical services?
2.	Review question	What is the clinical and cost effectiveness of different criteria for referral to epilepsy surgical services?
3.	Objective	Tailored epilepsy surgery is considered effective in the treatment of drug-resistant focal epilepsy in children and adults. Observational data evaluating trends over time reveal that referrals remain delayed despite the potential efficacy of epilepsy surgery. The aim of the review is to identify criteria for referral to epilepsy centres that offer comprehensive evaluation and surgery.
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language studies • Human studies The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Epilepsy
6.	Population	Inclusion: All children, young people and adults with epilepsy Exclusion: new-born babies (under 28 days)
7.	Intervention	Any referral criteria that have been evaluated

		Strata: none
8.	Comparator/Reference standard/Confounding factors	Other referral criteria
9.	Types of study to be included	RCT If no RCT data are available, non-randomised data will be considered. Prospective cohorts: no key confounders that have to be adjusted for have been identified, but the analysis report must demonstrate that it has tried to avoid bias arising from plausible potential confounders by an appropriate method such as regression/ANCOVA, stratification, or propensity matching. A study will be included. If all plausible confounders (for example epilepsy onset, classification of epilepsy, AED number) are shown to be reasonably matched at baseline. .
10.	Other exclusion criteria	Non-English language studies. Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	Randomised controlled trials and observational studies support the efficacy and safety of resective surgery for the treatment of drug-resistant epilepsy in appropriately selected individuals. Results from longitudinal studies, however, show a stagnant or declining rate of epilepsy surgery over time leading to an argument that epilepsy surgery remains underused despite evidence and guidelines supporting its use. It is important to better identify those people in whom surgery would be beneficial as there is a perception that even appropriate candidates for epilepsy surgery are being left for many years before being considered for this intervention.
12.	Primary outcomes (critical outcomes)	Appropriateness of referral decisions Appropriate, non-appropriate and non-appropriate non-referrals will be determined by study investigators. Follow-up time will be latest time point reported.
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately

		• a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.	
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.	
16.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/	
17.	Analysis of sub-groups	No subgroups	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic

		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date	May 2029	
22.	Anticipated completion date		
23.	Stage of review at time of this submission	Review stage	Started / Completed
		Preliminary searches	☐ / ☐
		Piloting of the study selection process	☐ / ☐
		Formal screening of search results against eligibility criteria	☐ / ☐
		Data extraction	☐ / ☐
		Risk of bias (quality) assessment	☐ / ☐
		Data analysis	☐ / ☐
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail epilepsies@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre	
25.	Review team members	The National Guideline Centre	
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.	
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in	

		line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10112/documents	
29.	Other registration details		
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Epilepsies, epilepsy, surgery, referral	
33.	Details of existing review of same topic by same authors		
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information		
36.	Details of final publication	www.nice.org.uk	

A.2 Review protocol for surgical interventions

ID	Field	Content
1.	Review title	What is the effectiveness of surgical intervention in epilepsy?
2.	Review question	What is the effectiveness of surgical intervention in epilepsy?
3.	Objective	Epilepsy surgery is appropriate for carefully selected patients with difficult-to-treat focal epilepsy. Surgery removes or alters the area of the brain where seizures originate. Estimates of the number of individuals with epilepsy who do not become seizure-free despite optimal drug therapy vary between at least 20% and up to 70%. Recent advances in neuroimaging and surgical techniques have improved the surgical treatments although it is estimated that surgery appears to be underused. The aim of the review is to determine the effectiveness of surgery in treatment-resistant epilepsy.
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Epilepsy is a disease characterized by an enduring predisposition in which brain activity becomes abnormal, causing seizures or periods of unusual behavior, sensations, and sometimes loss of awareness. Epilepsy is

		diagnosed after two unprovoked seizures or after a single seizure in people with an underlying cause that increases the risk of seizure recurrence.
6.	Population	Inclusion: People with treatment-resistant epilepsy Exclusion: New-born babies (under 28 days) with acute symptomatic seizures.
7.	Intervention	Resective surgery: - Temporal lobectomy - Extratemporal lobectomy(parietal/frontal/occipital/ insular) Disconnective surgery: - Callosotomy - Hemispherectomy, hemispherotomy. - Temporoparietal occipital disconnection - Hypothalamic hamartoma disconnection
8.	Comparator/Reference standard/Confounding factors	Medical management / usual care Wait-list control
9.	Types of study to be included	RCTs Systematic reviews of RCTs: For a systematic review to be included it must be conducted to the same methodological standard as NICE guideline reviews. If sufficient details are not provided to include a relevant systematic review, the review will only be used for citation searching. Non-randomised studies will be included if there is insufficient RCT evidence (less than or equal to 2 RCTs). Non-randomised studies will be considered if they adjust for key confounders (age and gender).
10.	Other exclusion criteria	• Non-English language studies. • Conference abstracts will be excluded because these do not typically provide sufficient information to fully assess risk of bias
11.	Context	There is an argument that epilepsy surgery remains underused, but the evidence to support this assertion is at times unclear. Results from longitudinal studies show a stagnant or declining rate of epilepsy surgery over time, despite the evidence and guidelines supporting its use.

12.	Primary outcomes (critical outcomes)	• Mortality at short-term follow-up of 12- 24 months and longer-term follow-up of >24-60 months • Seizure freedom (100% reduction in seizure frequency) at short-term follow-up of 12 to 24 months and longer-term follow-up of >24-60 months *Due to anticipated heterogeneity in reporting of seizure freedom, data will be extracted as presented within included studies. Where a study reports multiple variants then all data will be extracted. For decision making priority will be given to data presented as "time to 12 months seizure freedom", (i.e., time to event: HR or mean time) followed by "achievement of 12 months seizure freedom" (RR).* • Seizure frequency (50% or greater reduction in seizure frequency) at short-term follow-up of 12 to 24 months and longer-term follow-up of >24-60 month • Quality of life (measured with a validated scale) at short-term follow-up of 12 to 24 months and longer-term follow-up of >24-60 months • Healthcare resource use • Social functioning (measures of adaptive functioning or adaptive behaviour using a validated scale) short-term follow-up of 12 to 24 months and longer-term follow-up of >24-60 months • Cognitive outcomes (including neuropsychological measures of global cognitive functioning, executive functioning and memory using a validated scale) short-term follow-up of 12 to 24 months and longer-term follow-up of >24-60 months • In children and young people: neurodevelopmental outcomes (behavioural and emotional outcomes measured with a validated scale) short-term follow-up of 12 to 24 months and longer-term follow-up of >24-60 months • Serious adverse events (such as infection, stroke, severe bleeding)
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. EviBASE will be used for data extraction.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. Randomised controlled trials will be assessed with Cochrane RoB (2.0) and Systematic reviews will be assessed with Risk of Bias in Systematic Reviews (ROBIS) 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking:

		• papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.	
16.	Strategy for data synthesis	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Where meta-analysis is not possible, data will be presented, and quality assessed individually per outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random effects.	
17.	Analysis of sub-groups	In the presence of heterogeneity, sub-group analysis will be conducted: • according to the risk of bias of individual studies • by age (older people/adults/children) • study location (UK, US, Europe and rest of the world) • extra temporal vs temporal surgery • resection vs disconnection	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic

		☐	Prognostic	
		☐	Qualitative	
		☐	Epidemiologic	
		☐	Service Delivery	
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date			
22.	Anticipated completion date			
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☐	☑
		Piloting of the study selection process	☐	☑
		Formal screening of search results against eligibility criteria	☐	☑

		Data extraction	☐	☑
		Risk of bias (quality) assessment	☐	☑
		Data analysis	☐	☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail NGCEpilepsies@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of		

		Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10112/documents	
29.	Other registration details		
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Epilepsies, surgery	
33.	Details of existing review of same topic by same authors		
34.	Current review status	☐	Ongoing
		☒	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	[Provide any other information the review team feel is relevant to the registration of the review.]	
36.	Details of final publication	www.nice.org.uk	

A.3 Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2004, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2004 that were included in the previous guideline(s) will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[38] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with "Minor limitations" then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with "Very serious limitations" then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable).

	• OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2004 or later (including any such studies included in the previous guideline(s)) but that depend on unit costs and resource data entirely or predominantly from before 2004 will be rated as 'Not applicable'. • Studies published before 2004 (including any such studies included in the previous guideline(s)) will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B Literature search strategies

B.1 Surgical interventions

This literature search strategy was used for the following review:

- What is the effectiveness of surgical intervention in epilepsy?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[38]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 13: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 10 December 2020	Randomised controlled trials Systematic review studies Exclusions
Embase (OVID)	1974 – 10 December 2020	Randomised controlled trials Systematic review studies Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 issue 12 of 12 CENTRAL to 2020 Issue 12 of 12	None

Medline (Ovid) search terms

1.	exp epilepsy/
2.	seizures/
3.	exp status epilepticus/
4.	seizures, febrile/
5.	(dravet syndrome or epilep* or convuls* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	(epilep* adj4 (surg* or resect*)).ti,ab.
7.	or/1-5

8.	letter/
9.	editorial/
10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case report/
15.	(letter or comment*).ti.
16.	or/8-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or mouse or mice).ti.
25.	or/18-24
26.	7 not 25
27.	6 not 25
28.	Limit 26 to English language
29.	Limit 27 to English language
30.	exp surgery/ or exp neurosurgical procedures/
31.	((surg* or operat* or procedure*) adj3 (neurological or resect* or disconnect* or extratemporal or temporal or TLE)).ti,ab.
32.	exp Hemispherectomy/
33.	(hemispherectomy or hemispherotomy).ti,ab.
34.	(temporo-occipito-parietal* or temporal occipital parietal*).ti,ab.
35.	(corpus callosotomy or corpus callosum transect* or subpial transect* or amygdalotomy or lobect* or topect* or corticectomy or amygdalohippocampectomy).ti,ab.
36.	lesionectomy.ti,ab.
37.	(laser ablation or thermal ablation or laser interstitial thermal therapy or LITT or hypothalamic hamartoma disconnect*).ti,ab.
38.	or/30-37
39.	randomized controlled trial.pt.
40.	controlled clinical trial.pt.
41.	randomi#ed.ti,ab.
42.	placebo.ab.
43.	randomly.ti,ab.
44.	Clinical Trials as topic.sh.
45.	trial.ti.
46.	or/39-45
47.	Meta-Analysis/
48.	exp Meta-Analysis as Topic/
49.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
50.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
51.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.

52.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
53.	(search* adj4 literature).ab.
54.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
55.	cochrane.jw.
56.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
57.	or/47-56
58.	28 and 38 and (46 or 57)
59.	29 and (46 or 57)
60.	58 or 59

Embase (Ovid) search terms

1.	exp epilepsy/
2.	seizure/
3.	epileptic state/
4.	febrile convulsion/
5.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	(epilep* adj4 (surg* or resect*)).ti,ab.
7.	or/1-5
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	case report/ or case study/
12.	(letter or comment*).ti.
13.	or/8-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animal/ not human/
17.	nonhuman/
18.	exp Animal Experiment/
19.	exp Experimental Animal/
20.	animal model/
21.	exp Rodent/
22.	(rat or rats or mouse or mice).ti.
23.	or/15-22
24.	7 not 23
25.	6 not 23
26.	limit 24 to English language
27.	limit 25 to English language
28.	surgery/
29.	exp brain surgery/
30.	((surg* or operat* or procedure*) adj3 (neurological or resect* or disconnect* or extratemporal or temporal or TLE)).ti,ab.
31.	exp hemispherectomy/
32.	(hemispherectomy or hemispherotomy).ti,ab.
33.	(temporo-occipito-parietal* or temporal occipital parietal*).ti,ab.

34.	(corpus callosotomy or corpus callosum transect* or subpial transect* or amygdalotomy or lobect* or topect* or corticectomy or amygdalohippocampectomy).ti,ab.
35.	lesionectomy.ti,ab.
36.	(laser ablation or thermal ablation or laser interstitial thermal therapy or LITT or hypothalamic hamartoma disconnect*).ti,ab.
37.	or/28-36
38.	random*.ti,ab.
39.	factorial*.ti,ab.
40.	(crossover* or cross over*).ti,ab.
41.	((doubl* or singl*) adj blind*).ti,ab.
42.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
43.	crossover procedure/
44.	single blind procedure/
45.	randomized controlled trial/
46.	double blind procedure/
47.	or/38-46
48.	systematic review/
49.	meta-analysis/
50.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
51.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
52.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
53.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
54.	(search* adj4 literature).ab.
55.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
56.	cochrane.jw.
57.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
58.	or/48-57
59.	26 and 37 and (47 or 58)
60.	27 and (47 or 58)
61.	59 or 60

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Epilepsy] explode all trees
#2.	MeSH descriptor: [Seizures] explode all trees
#3.	MeSH descriptor: [Status Epilepticus] explode all trees
#4.	MeSH descriptor: [Seizures, Febrile] explode all trees
#5.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome):ti,ab
#6.	(epilep* near/4 (surg* or resect*)):ti,ab
#7.	(or #1-#5)
#8.	MeSH descriptor: [Neurosurgical Procedures] explode all trees
#9.	MeSH descriptor: [Hemispherectomy] explode all trees
#10.	MeSH descriptor: [Anterior Temporal Lobectomy] explode all trees
#11.	((surg* or operat* or procedure*) near/3 (neurological or resect* or disconnect* or extratemporal or temporal or TLE)):ti,ab

#12.	(hemispherectomy or hemispherotomy):ti,ab
#13.	(temporo-occipito-parietal* or temporal occipital parietal*):ti,ab
#14.	(corpus callosotomy or corpus callosum transect* or subpial transect* or amygdalotomy or lobect* or topect* or corticectomy or amygdalohippocampectomy):ti,ab
#15.	lesionectomy:ti,ab
#16.	(laser ablation or thermal ablation or laser interstitial thermal therapy or LITT or hypothalamic hamartoma disconnect*):ti,ab
#17.	(or #8-#16)
#18.	#6 and #17
#19.	#7 and #17
#20.	#18 or #19

B.1.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to an Epilepsies population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics and quality of life studies.

Table 14: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	Health Economics 1 January 2014 – 13 May 2021 Quality of Life 1946 – 13 May 2021	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments)
Embase	Health Economics 1 January 2014 – 13 May 2021 Quality of Life 1974 – 13 May 2021	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments)
Centre for Research and Dissemination (CRD)	HTA - Inception – 13 May 2021 NHSEED - Inception to 31 March 2015	None

Medline (Ovid) search terms

1.	exp epilepsy/
2.	seizures/
3.	exp status epilepticus/
4.	seizures, febrile/
5.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/

11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	quality-adjusted life years/
45.	sickness impact profile/
46.	(quality adj2 (wellbeing or well being)).ti,ab.
47.	sickness impact profile.ti,ab.
48.	disability adjusted life.ti,ab.
49.	(qal* or qtime* or qwb* or daly*).ti,ab.
50.	(euroqol* or eq5d* or eq 5*).ti,ab.
51.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
52.	(hui or hui1 or hui2 or hui3).ti,ab.
53.	(health* year* equivalent* or hye or hyes).ti,ab.
54.	discrete choice*.ti,ab.
55.	rosser.ti,ab.
56.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.

57.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
58.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
59.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
60.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
61.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
62.	or/44-61
63.	26 and (43 or 62)

Embase (Ovid) search terms

1.	exp *epilepsy/
2.	*landau kleffner syndrome/
3.	exp *seizure/
4.	"seizure, epilepsy and convulsion"/
5.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	6 not 22
24.	limit 23 to English language
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.

36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	quality adjusted life year/
40.	sickness impact profile/
41.	(quality adj2 (wellbeing or well being)).ti,ab.
42.	sickness impact profile.ti,ab.
43.	disability adjusted life.ti,ab.
44.	(qal* or qtime* or qwb* or daly*).ti,ab.
45.	(euroqol* or eq5d* or eq 5*).ti,ab.
46.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
47.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
48.	(hui or hui1 or hui2 or hui3).ti,ab.
49.	(health* year* equivalent* or hye or hyes).ti,ab.
50.	discrete choice*.ti,ab.
51.	rosser.ti,ab.
52.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
53.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
54.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
55.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
56.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
57.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
58.	or/39-57
59.	24 and (38 or 58)

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Epilepsy EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Seizures EXPLODE ALL TREES
#3.	MeSH DESCRIPTOR Status Epilepticus EXPLODE ALL TREES
#4.	MeSH DESCRIPTOR Seizures, Febrile EXPLODE ALL TREES
#5.	((dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome))
#6.	#1 OR #2 OR #3 OR #4 OR #5

B.2 Referral for surgery

This literature search strategy was used for the following review:

- What is the clinical and cost effectiveness of different criteria for referral to epilepsy surgical services?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[38]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.2.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 15: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 04 August 2020	Randomised controlled trials Systematic review studies Exclusions
Embase (OVID)	1974 – 04 August 2020	Randomised controlled trials Systematic review studies Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 8 of 12 CENTRAL to 2020 Issue 8 of 12	None

Medline (Ovid) search terms

61.	exp epilepsy/
62.	seizures/
63.	exp status epilepticus/
64.	seizures, febrile/
65.	(dravet syndrome or epilep* or convuls* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
66.	or/1-5
67.	letter/
68.	editorial/
69.	news/
70.	exp historical article/
71.	Anecdotes as Topic/
72.	comment/
73.	case report/
74.	(letter or comment*).ti.
75.	or/7-14
76.	randomized controlled trial/ or random*.ti,ab.
77.	15 not 16
78.	animals/ not humans/
79.	exp Animals, Laboratory/
80.	exp Animal Experimentation/
81.	exp Models, Animal/
82.	exp Rodentia/
83.	(rat or rats or mouse or mice).ti.
84.	or/17-23

85.	6 not 24
86.	limit 25 to English language
87.	exp "referral and consultation"/
88.	(refer or referr* or consult*).ti,ab.
89.	((presurgical or pre-surgical or surg* or neurosurg*) adj2 (assessment* or evaluation* or decision* or criteria*)).ti,ab.
90.	((decision* or criteria* or appropriate or non-appropriate or inappropriate or approv* or non approv* or underutiliz* or underutilis* or misconception* or misperception*) adj2 (surg* or neurosurg*)).ti,ab.
91.	*Drug Resistance/
92.	(drug adj resist*).ti,ab.
93.	exp *Electroencephalography/
94.	((electroencephalogra* or EEG) adj (data or spike* or discharge*)).ti,ab.
95.	exp *Magnetic Resonance Imaging/
96.	*Single Photon Emission Computed Tomography Computed Tomography/
97.	*Positron Emission Tomography Computed Tomography/
98.	((magnetic resonance Imag* or MRI* or PET or SPECT or tomograph*) adj (data or result*)).ti,ab.
99.	(history adj2 (head injur* or seiz*)).ti,ab.
100.	(surg* adj2 (service* or centre* or center* or clinic*1)).ti,ab.
101.	or/27-40
102.	26 and 41
103.	randomized controlled trial.pt.
104.	controlled clinical trial.pt.
105.	randomi#ed.ti,ab.
106.	placebo.ab.
107.	randomly.ti,ab.
108.	Clinical Trials as topic.sh.
109.	trial.ti.
110.	or/43-49
111.	Meta-Analysis/
112.	exp Meta-Analysis as Topic/
113.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
114.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
115.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
116.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
117.	(search* adj4 literature).ab.
118.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
119.	cochrane.jw.
120.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
121.	or/51-60
122.	42 and (50 or 61)

Embase (Ovid) search terms

62.	exp epilepsy/
63.	seizure/

64.	epileptic state/
65.	febrile convulsion/
66.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
67.	or/1-5
68.	letter.pt. or letter/
69.	note.pt.
70.	editorial.pt.
71.	case report/ or case study/
72.	(letter or comment*).ti.
73.	or/7-11
74.	randomized controlled trial/ or random*.ti,ab.
75.	12 not 13
76.	animal/ not human/
77.	nonhuman/
78.	exp Animal Experiment/
79.	exp Experimental Animal/
80.	animal model/
81.	exp Rodent/
82.	(rat or rats or mouse or mice).ti.
83.	or/14-21
84.	6 not 22
85.	limit 23 to English language
86.	random*.ti,ab.
87.	factorial*.ti,ab.
88.	(crossover* or cross over*).ti,ab.
89.	((doubl* or singl*) adj blind*).ti,ab.
90.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
91.	crossover procedure/
92.	single blind procedure/
93.	randomized controlled trial/
94.	double blind procedure/
95.	or/25-33
96.	systematic review/
97.	meta-analysis/
98.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
99.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
100.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
101.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
102.	(search* adj4 literature).ab.
103.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
104.	cochrane.jw.
105.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
106.	or/35-44

107.	exp patient referral/
108.	(refer or referr* or consult*).ti,ab.
109.	((presurgical or pre-surgical or surg* or neurosurg*) adj2 (assessment* or evaluation* or decision* or criteria*)).ti,ab.
110.	((decision* or criteria* or appropriate or non-appropriate or inappropriate or approv* or non approv* or underutiliz* or underutilis* or misconception* or misperception*) adj2 (surg* or neurosurg*)).ti,ab.
111.	*drug resistance/
112.	(drug adj resist*).ti,ab.
113.	exp *electroencephalography/
114.	((electroencephalogra* or EEG) adj (data or spike* or discharge*)).ti,ab.
115.	*nuclear magnetic resonance imaging/
116.	*Single Photon Emission Computed Tomography Computed Tomography/
117.	*positron emission tomography-computed tomography/
118.	((magnetic resonance Imag* or MRI* or PET or SPECT or tomograph*) adj (data or result*)).ti,ab.
119.	(history adj2 (head injur* or seiz*)).ti,ab.
120.	(surg* adj2 (service* or centre* or center* or clinic*1)).ti,ab.
121.	or/46-59
122.	24 and 60
123.	61 and (34 or 45)

Cochrane Library (Wiley) search terms

#21.	MeSH descriptor: [Epilepsy] explode all trees
#22.	MeSH descriptor: [Seizures] this term only
#23.	MeSH descriptor: [Status Epilepticus] explode all trees
#24.	MeSH descriptor: [Seizures, Febrile] this term only
#25.	(dravet syndrome or epilep* or convuls* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome):ti,ab
#26.	(or #1-#5)
#27.	MeSH descriptor: [Referral and Consultation] explode all trees
#28.	(refer or referr* or consult*):ti,ab
#29.	((presurgical or pre-surgical or surg* or neurosurg*) near/2 (assessment* or evaluation* or decision* or criteria*)):ti,ab
#30.	((decision* or criteria* or appropriate or non-appropriate or inappropriate or approv* or non approv* or underutiliz* or underutilis* or misconception* or misperception*) near/2 (surg* or neurosurg*)):ti,ab
#31.	MeSH descriptor: [Drug Resistance] explode all trees
#32.	(drug near/1 resist*):ti,ab
#33.	MeSH descriptor: [Electroencephalography] explode all trees
#34.	((electroencephalogra* or EEG) near/1 (data or spike* or discharge*)):ti,ab
#35.	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
#36.	MeSH descriptor: [Single Photon Emission Computed Tomography Computed Tomography] explode all trees
#37.	MeSH descriptor: [Positron Emission Tomography Computed Tomography] explode all trees
#38.	((magnetic resonance Imag* or MRI* or PET or SPECT or tomograph*) near/1 (data or result*)):ti,ab
#39.	(history near/2 (head injur* or seiz*)):ti,ab

#40.	(surg* near/2 (service* or centre* or center* or clinic*1)):ti,ab
#41.	(or #7-#20)
#42.	#6 and #21

B.2.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to an Epilepsies population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics and quality of life studies.

Table 16: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	Health Economics 1 January 2014 – 13 May 2021 Quality of Life 1946 – 13 May 2021	Health economics studies Quality of life studies Exclusions
Embase	Health Economics 1 January 2014 – 13 May 2021 Quality of Life 1974 – 13 May 2021	Health economics studies Quality of life studies Exclusions
Centre for Research and Dissemination (CRD)	HTA - Inception – 13 May 2021 NHSEED - Inception to 31 March 2015	None

Medline (Ovid) search terms

64.	exp epilepsy/
65.	seizures/
66.	exp status epilepticus/
67.	seizures, febrile/
68.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
69.	or/1-5
70.	letter/
71.	editorial/
72.	news/
73.	exp historical article/
74.	Anecdotes as Topic/
75.	comment/
76.	case report/
77.	(letter or comment*).ti.
78.	or/7-14
79.	randomized controlled trial/ or random*.ti,ab.
80.	15 not 16

81.	animals/ not humans/
82.	exp Animals, Laboratory/
83.	exp Animal Experimentation/
84.	exp Models, Animal/
85.	exp Rodentia/
86.	(rat or rats or mouse or mice).ti.
87.	or/17-23
88.	6 not 24
89.	limit 25 to English language
90.	Economics/
91.	Value of life/
92.	exp "Costs and Cost Analysis"/
93.	exp Economics, Hospital/
94.	exp Economics, Medical/
95.	Economics, Nursing/
96.	Economics, Pharmaceutical/
97.	exp "Fees and Charges"/
98.	exp Budgets/
99.	budget*.ti,ab.
100.	cost*.ti.
101.	(economic* or pharmaco?economic*).ti.
102.	(price* or pricing*).ti,ab.
103.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
104.	(financ* or fee or fees).ti,ab.
105.	(value adj2 (money or monetary)).ti,ab.
106.	or/27-42
107.	quality-adjusted life years/
108.	sickness impact profile/
109.	(quality adj2 (wellbeing or well being)).ti,ab.
110.	sickness impact profile.ti,ab.
111.	disability adjusted life.ti,ab.
112.	(qal* or qtime* or qwb* or daly*).ti,ab.
113.	(euroqol* or eq5d* or eq 5*).ti,ab.
114.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
115.	(hui or hui1 or hui2 or hui3).ti,ab.
116.	(health* year* equivalent* or hye or hyes).ti,ab.
117.	discrete choice*.ti,ab.
118.	rosser.ti,ab.
119.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
120.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
121.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
122.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
123.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
124.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
125.	or/44-61
126.	26 and (43 or 62)

Embase (Ovid) search terms

60.	exp *epilepsy/
61.	*landau kleffner syndrome/
62.	exp *seizure/
63.	"seizure, epilepsy and convulsion"/
64.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
65.	or/1-5
66.	letter.pt. or letter/
67.	note.pt.
68.	editorial.pt.
69.	case report/ or case study/
70.	(letter or comment*).ti.
71.	or/7-11
72.	randomized controlled trial/ or random*.ti,ab.
73.	12 not 13
74.	animal/ not human/
75.	nonhuman/
76.	exp Animal Experiment/
77.	exp Experimental Animal/
78.	animal model/
79.	exp Rodent/
80.	(rat or rats or mouse or mice).ti.
81.	or/15-21
82.	6 not 22
83.	limit 23 to English language
84.	health economics/
85.	exp economic evaluation/
86.	exp health care cost/
87.	exp fee/
88.	budget/
89.	funding/
90.	budget*.ti,ab.
91.	cost*.ti.
92.	(economic* or pharmaco?economic*).ti.
93.	(price* or pricing*).ti,ab.
94.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
95.	(financ* or fee or fees).ti,ab.
96.	(value adj2 (money or monetary)).ti,ab.
97.	or/25-37
98.	quality adjusted life year/
99.	sickness impact profile/
100.	(quality adj2 (wellbeing or well being)).ti,ab.
101.	sickness impact profile.ti,ab.
102.	disability adjusted life.ti,ab.

103.	(qal* or qtime* or qwb* or daly*).ti,ab.
104.	(euroqol* or eq5d* or eq 5*).ti,ab.
105.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
106.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
107.	(hui or hui1 or hui2 or hui3).ti,ab.
108.	(health* year* equivalent* or hye or hyes).ti,ab.
109.	discrete choice*.ti,ab.
110.	rosser.ti,ab.
111.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
112.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
113.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
114.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
115.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
116.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
117.	or/39-57
118.	24 and (38 or 58)

NHS EED and HTA (CRD) search terms

#7.	MeSH DESCRIPTOR Epilepsy EXPLODE ALL TREES
#8.	MeSH DESCRIPTOR Seizures EXPLODE ALL TREES
#9.	MeSH DESCRIPTOR Status Epilepticus EXPLODE ALL TREES
#10.	MeSH DESCRIPTOR Seizures, Febrile EXPLODE ALL TREES
#11.	((dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome))
#12.	#1 OR #2 OR #3 OR #4 OR #5

Appendix C Effectiveness evidence study selection

Figure 3: Flow chart of clinical study selection for the review of referral for surgery

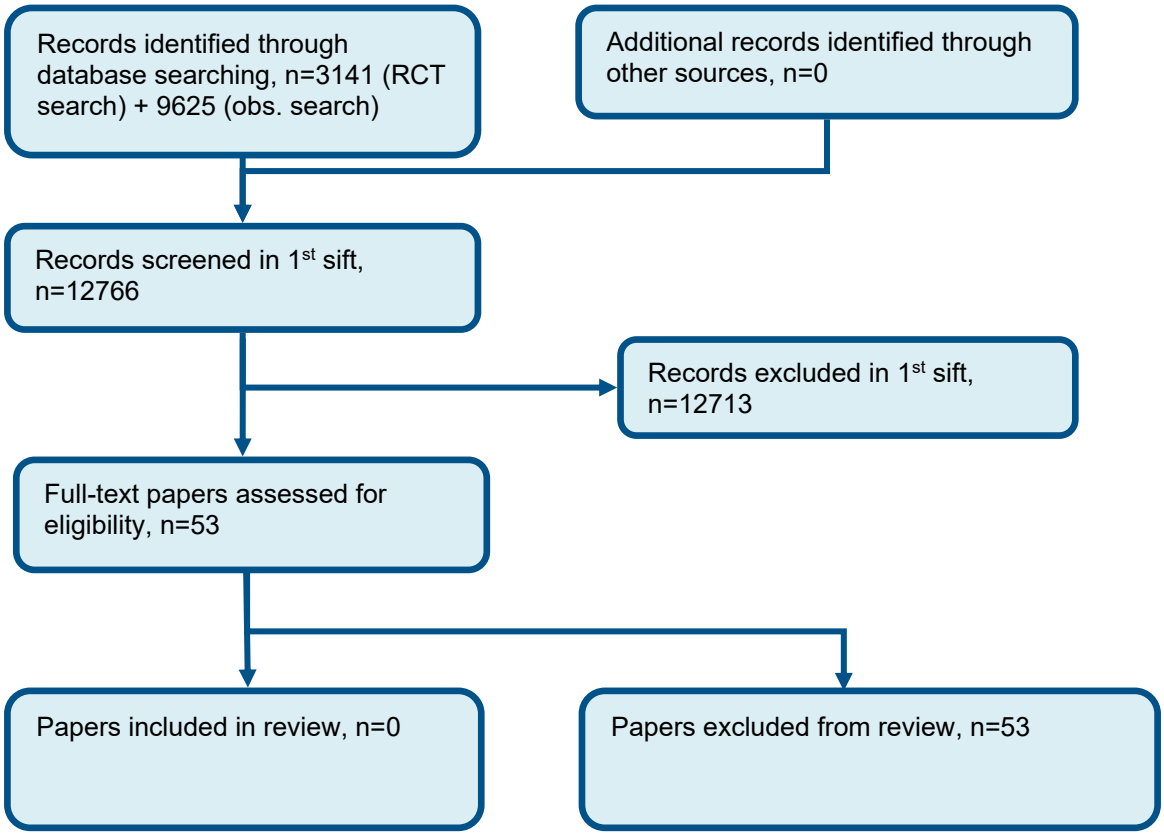
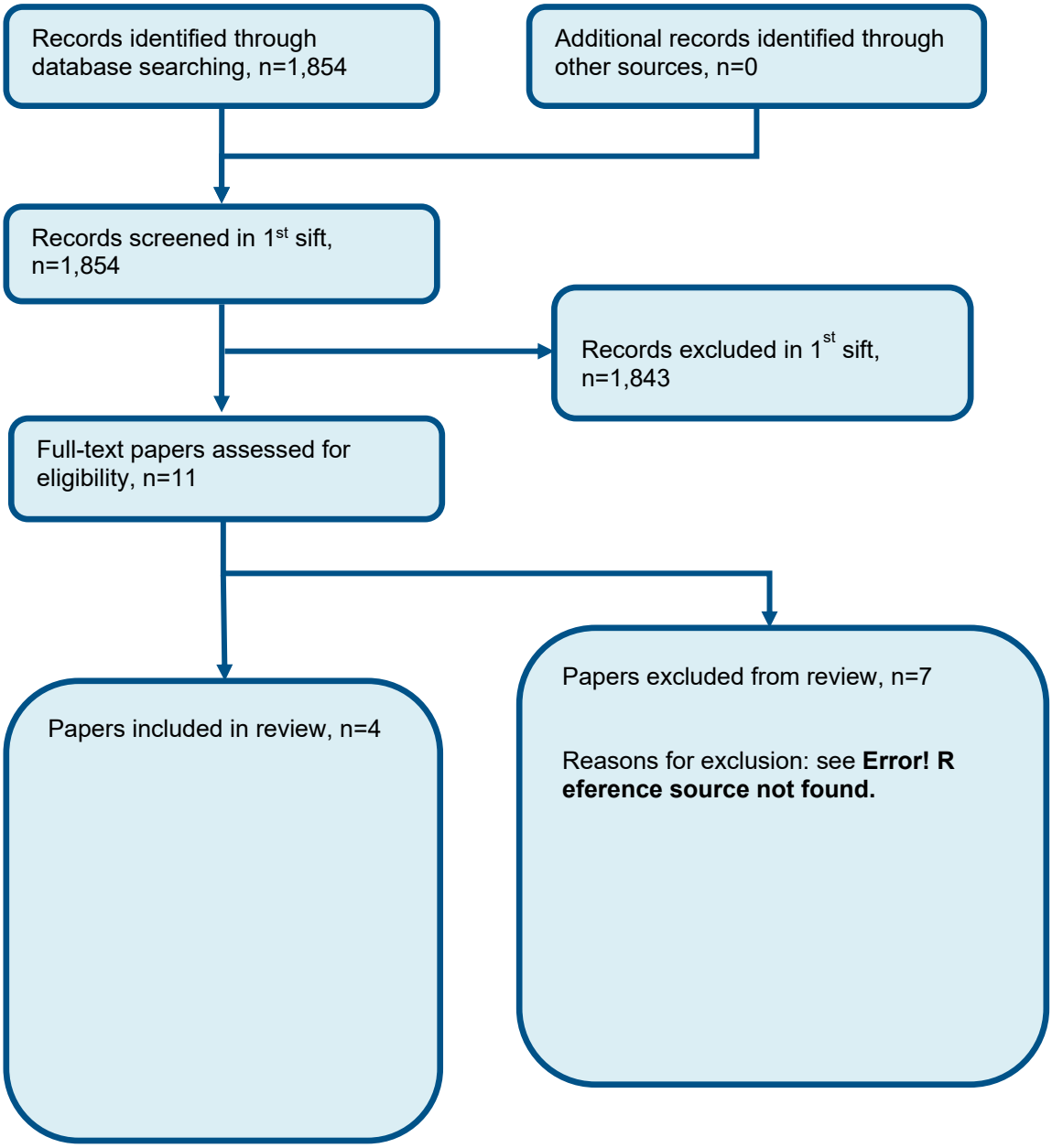
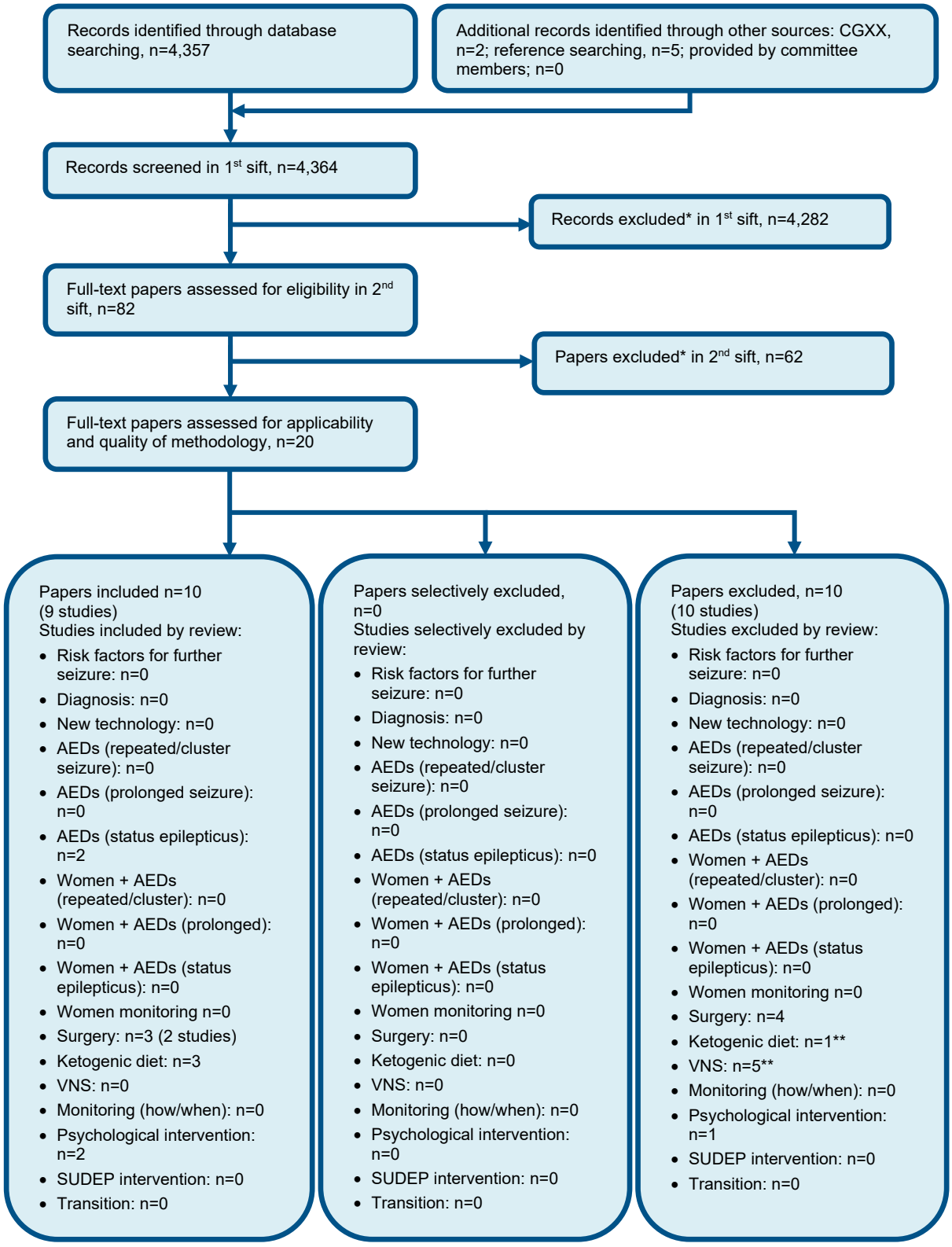


Figure 4: Flow chart of clinical study selection for the review of surgical interventions



Appendix D Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language
**Please note that 1 article related to two questions. For this reason, the numbers listed for each review may not total the number of full text articles assessed for applicability and quality of methodology.

Appendix E Economic evidence tables

None.

Appendix F Health economic model

No original economic modelling was undertaken for this review question.

Appendix G Excluded studies

G.1 Referral to surgery

G.1.1 Studies excluded from the clinical review

Study	Exclusion reason
Ansari 2010[3]	Review - references checked
Bazil 2012[4]	Review - references checked
Conte 2019[15]	non comparative; wrong outcomes
Englot 2013[20]	Review - references checked
Gloss 2017[22]	Not review population. Not guideline condition. Inappropriate comparison. Incorrect interventions. Review - references checked
Holler 2015[24]	Review - references checked
Janszky 2010[26]	Review - references checked
Jardim 2016[27]	wrong outcomes
Jehi 2015[28]	no useable outcomes. non comparative
Kwan 2009[30]	Review - references checked
Kwon 2016[32]	Review - references checked
Kwon 2020[31]	Review - references checked
Malhotra 2016[35]	no useable outcomes. non comparative
Negishi 2011[39]	no useable outcomes. non comparative
Newberg 2000[40]	No useable outcomes
Nguyen 2013[41]	conference abstract
Obaid 2017[45]	conference abstract
Panebianco 2015[48]	Incorrect interventions. Inappropriate comparison. Systematic review - references checked
Patil 2008[49]	no useable outcomes. non comparative
Pindrik 2018[51]	Review - references checked
Punia 2018[52]	Review - references checked
Ramanujam 2017[53]	no useable outcomes
Ryvlin 1998[54]	no useable outcomes
Ryvlin 2008[55]	Review - references checked
Ryvlin 2016[56]	SR - references checked
Salam 2014[57]	conference abstract
Schmidt 2004[59]	SR - references checked
See 2013[60]	No useable outcomes
Seghezzi 2013[61]	conference abstract
Sellner 2013[62]	Review - references checked
Sisodiya 1997[63]	no useable outcomes
Steinbrenner 2019[68]	no useable outcomes. non comparative

Struck 2011[69]	no useable outcomes. >1 comparator but not used in independent groups
Stylianou 2016[70]	SR - references checked
Suarez-pinera 2015[71]	No useable outcomes
Sutherling 2008[72]	No useable outcomes
Szaflarski 2017[73]	Review - references checked
Uijl 2008[75]	no useable outcomes. non comparative
Uijl 2008[76]	no useable outcomes. non comparative
Vickrey 1995[79]	No useable outcomes
Vickrey 1997[78]	No useable outcomes
Wang 2019[80]	Review - references checked
Wiebe 2012[84]	SR - references checked
Willmann 2007[87]	Review - references checked
Wright 2016[88]	conference abstract
Yan 2019[89]	Review - references checked
Yang 2015[90]	Review - references checked
Yin 2013[91]	Review - references checked
Zhang 2013[93]	No useable outcomes
Zhang 2014[94]	Review - references checked
Zhang 2015[92]	Review - references checked

G.1.2 Health Economic studies - referral

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2004 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Studies excluded from the health economic review

Reference	Reason for exclusion
None.	

G.2 Surgical interventions

G.2.1 Studies excluded from the clinical review

Study	Reason for exclusion
Alexiades 2018[1]	Not RCT, commentary
Bien 2001[5]	Not RCT, non-randomised study
Bien 2006[6]	Not RCT, non-randomised study
Chan 2019[13]	Systematic review did not match protocol
Ding 2016[17]	Not RCT, non-randomised study
West 2019[81]	Systematic review did not match protocol
Wiebe 2009[85]	Not RCT, commentary

G.2.2 Health Economic studies – surgical interventions

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2004 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Studies excluded from the health economic review

Reference	Reason for exclusion
Bowen 2012[9]	This was a Canadian cost utility analysis. Excluded because based on retrospective observational data.
Picot 2016[50]	Excluded because based on retrospective observational data.
Widjaja 2011[82]	Excluded because based on retrospective observational data.
Catchpool 2019[12]	This was an Australian cost-utility analysis. Excluded because effectiveness evidence is partly based on observational data excluded from clinical review and expert opinion. HRQoL based on expert opinion. In addition, concerns with short time horizon, model structure, exclusion of presurgical evaluation costs and it was unclear if discounting was applied.

Appendix H Effectiveness evidence

Study	Dwivedi 2017[18]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=116)
Countries and setting	Conducted in India
Line of therapy	1st line
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Children, young people and adults with confirmed pharmacoresistant epilepsy
Subgroup analysis within study	Not applicable
Inclusion criteria	18 years of age or younger with drug-resistant epilepsy to undergo brain surgery appropriate to the underlying cause of epilepsy along with appropriate medical therapy (surgery group, 57 patients) or to receive medical therapy alone (medical-therapy group, 59 patients). 1) Patients with intractable (drug refractory) epilepsy with the age ≤ 18 years. 2) Subjects with seizure frequency >1/month or if seizures are not controlled by two or more appropriate AEDs used in their optimal doses, 3) All subjects who have epileptic encephalopathy, infantile spasm, disabling seizures. 4) All patients who will receive the clearance for epilepsy surgery by the surgery team, after a multidisciplinary case conference in Paediatrics neurology, AIIMS. 5) All patients and their legal authorized representatives (LAR) who have given consent for participation.
Exclusion criteria	1) All patients with underlying metabolic abnormality, cardiac abnormality, renal failure and respiratory disease. 2) Those patients with history of status epilepticus, requiring early or immediate surgery (as these are not put in wait list). 3) Age >18 years. 4) All patients who do not agree to follow up or consent to participation. Patients were not included in the trial if there was no consensus regarding the location of an epileptic focus and were excluded if

Study	Dwivedi 2017[18]
	there were metabolic abnormalities (genetic or acquired) or cardiac, renal, or any other systemic illness or a history of status epilepticus. In all the patients in the surgery group, post-surgery MRI was performed with a high-field 1.5 Tesla system in the operating room to ensure the adequacy of the planned excision.
Age, gender and ethnicity	Age - Median (range): surgery - 9 years (0.8 to 17), medical - 10 years (2 to 17). Gender (M:F): 42 female, 74 male. Ethnicity: Not stated.
Further population details	1. Children and young people: Children and young people 2. Girls and women of who are able to get pregnant (including those who are pregnant and breastfeeding): 3. Older people: 4. People with learning disabilities: 5. Type of epilepsy:
Indirectness of population	No indirectness
Interventions	(n=57) Intervention 1: Surgical intervention. Surgery - Patients with concordance of video EEG localization of the region of onset of the seizure (ictal-onset zone) and the location of the lesion on MRI underwent resection of that region of cortex or of the lesion or malformed cortex; those with multiple, subtle, or no lesions underwent resection of the region that was concordant between video EEG results and localization on PET, SPECT, or MEG. Patients who had multiple seizure types (including drop attacks) and multiple bilateral lesions and seizure foci underwent corpus callosotomy. Patients who had extensive lesions confined to one hemisphere with significant weakness of limbs (weak pincer grip or worse) opposite to the involved hemisphere underwent hemispherotomy. Duration 1 year. Concurrent medication/care: All the patients continued to receive antiepileptic drugs, and changes were made by the treating clinicians as necessary to manage seizures. Indirectness: No indirectness (n=59) Intervention 2: Wait-list control. Medical therapy group - The patients in the medical-therapy group were assigned to a waiting list for surgery. Duration 1 year. Concurrent medication/care: All the patients continued to receive antiepileptic drugs, and changes were made by the treating clinicians as necessary to manage seizures. Indirectness: No indirectness
Funding	Academic or government funding (Supported by a grant (5/4-5/Neuro/2010-NCD-I) from the Indian Council of Medical Research, with the collaboration of the Center of Excellence for Epilepsy and Magnetoencephalography Center and a grant (BT/01/COE/09/08) from the Department of Biotechnology, Government of India, to the All-India Institute of

Study	Dwivedi 2017[18]
	Medical Sciences of New Delhi and the National Brain Research Center.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SURGICAL INTERVENTION versus WAIT-LIST CONTROL

Protocol outcome 1: Quality of life at 12-24 months at 12-24 months
- Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Total score on Paediatric Quality of Life Inventory at 1 year; Group 1: mean 76.1 (SD 13.1); n=57, Group 2: mean 53.9 (SD 18.5); n=59
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: types of seizure (surgery/medical); focal - 75%/73%, secondary generalised - 25%/27%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 1, Reason: lost to follow up

Protocol outcome 2: Mortality at 12-24 months at 12-24 months
- Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Mortality at 1 year; Group 1: 0/57, Group 2: 0/59
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: types of seizure (surgery/medical); focal - 75%/73%, secondary generalised - 25%/27%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 1, Reason: lost to follow up

Protocol outcome 3: First seizure at 12- 24 months at 12- 24 months
- Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: first seizure at 1 year; HR: 0.283 (95% CI: 0.184-0.436)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: types of seizure (surgery/medical); focal - 75%/73%, secondary generalised - 25%/27%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 1, Reason: lost to follow up

Protocol outcome 4: Social functioning (measures of adaptive functioning or adaptive behaviour using a validated scale) at 12- 24 months at 12- 24 months
- Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Total score on Child Behaviour Checklist at 1 year; Group 1: mean 57.2 (SD 6.7); n=57, Group 2: mean 68.6 (SD 7.6); n=59; Comments: normal score, <60; borderline, 60 to 63; and clinically impaired, >63
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: types of seizure (surgery/medical); focal - 75%/73%, secondary generalised - 25%/27%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 1, Reason: lost to follow up

Protocol outcome 5: In children and young people: neurodevelopmental outcomes (behavioural and emotional outcomes measured with a validated scale) at 12- 24 months at 12- 24 months
- Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Intelligence quotient on Binet-Kamat test at 1 year; Group 1: mean 62.7 (SD 18.5); n=57, Group 2: mean 58.9 (SD 22.1); n=59

Study	**Dwivedi 2017[18]**
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: types of seizure (surgery/medical); focal - 75%/73%, secondary generalised - 25%/27%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 1, Reason: lost to follow up Protocol outcome 6: Adverse events (such as infection, stroke, severe bleeding) at N/A - Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Serious adverse events at 1 year; Group 1: 19/57, Group 2: 0/59 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: types of seizure (surgery/medical); focal - 75%/73%, secondary generalised - 25%/27%; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 1, Reason: lost to follow up	
Protocol outcomes not reported by the study	Quality of life at>24-60 months at >24-60 months; Mortality at >24-60 months at >24-60 months; Seizure freedom (100% reduction in seizure frequency) at >24-60 months at >24-60 months; Seizure frequency (50% or greater reduction in seizure frequency) at 12- 24 months at 12- 24 months; Seizure frequency (50% or greater reduction in seizure frequency) at >24-60 months at >24-60 months; Healthcare resource use at N/A; Social functioning (measures of adaptive functioning or adaptive behaviour using a validated scale) at >24-60 months at >24-60 months; Cognitive outcomes (including neuropsychological measures of global cognitive functioning, executive functioning and memory using a validated scale) at 12- 24 months at 12- 24 months; Cognitive outcomes (including neuropsychological measures of global cognitive functioning, executive functioning and memory using a validated scale) at >24-60 months at >24-60 months; In children and young people: neurodevelopmental outcomes (behavioural and emotional outcomes measured with a validated scale) at >24-60 months at >24-60 months.

Study	**Engel 2012[19]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=38)
Countries and setting	Conducted in USA
Line of therapy	1st line

Study	Engel 2012[19]
Duration of study	Intervention + follow up: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Children, young people and adults with confirmed pharmacoresistant epilepsy
Subgroup analysis within study	Not applicable
Inclusion criteria	Participants were males and females aged 12 years or older with mesial TLE (MTLE) and disabling seizures that had persisted for no more than 2 consecutive years following adequate trials of 2 brand name AEDs. Participants had to be considered candidates for anteromesial temporal resection based on a standardized presurgical evaluation protocol.
Exclusion criteria	Exclusion criteria included a history of serious cerebral insult after the age of 5, a progressive neurological disorder, psychogenic non epileptic seizures, focal neurologic deficits other than memory disturbances, > 4 secondarily generalized seizures per year for > 3 years, or more than one episode of status epilepticus other than febrile status epilepticus. The latter 2 exclusionary criteria were felt to stretch the definition of “early”. Surgical candidacy was determined by a standardized diagnostic protocol consisting of inpatient video-EEG monitoring, structural MRI, FDG-PET, and neuropsychological and neuropsychiatric evaluations.
Age, gender and ethnicity	Age - Mean (SD): medical - 30.9 (10.1), surgical - 37.5 (11.1). Gender (M:F): 18 male, 20 female. Ethnicity: 29 white, 6 black, 3 other
Further population details	1. Children and young people: Children and young people 2. Girls and women of who are able to get pregnant (including those who are pregnant and breastfeeding): 3. Older people: 4. People with learning disabilities: 5. Type of epilepsy:
Extra comments	. All participants randomized to surgery also underwent a bilateral intracarotid amobarbital procedure.
Indirectness of population	No indirectness
Interventions	(n=23) Intervention 1: Usual care . AED treatment - The objectives of pharmacotherapy were to achieve and maintain a seizure free state and minimize adverse effects. Duration 2 years. Concurrent medication/care: The same protocol was used for both treatment groups and reflected current practice used in most US epilepsy centers. It consisted of 4 stages: (1)monotherapy;(2)ditherapy;(3)optional treatment with rarely used AEDs;

Study	Engel 2012[19]
	and(4) treatment with multiple AEDs. Generic drugs were not permitted. Pharmacotherapy for seizures for both study groups was monitored by an independent panel of AED clinical pharmacology experts who were blinded to treatment assignment. . Indirectness: No indirectness (n=15) Intervention 2: Surgical intervention. Surgery - All sites utilized the same anteromesial temporal resection, which consisted of en bloc resection of the anterior 3.5 to 4 cm (in the dominant and non-dominant hemispheres, respectively) of the lateral temporal lobe,sparing the superior temporal gyrus, followed by removal of the mesial structures including en bloc resection of the hippocampus and resection of parahippocampal gyrus and part of the amygdala. Duration 2 years. Concurrent medication/care: The same protocol was used for both treatment groups and reflected current practice used in most US epilepsy centers. It consisted of 4 stages: (1)monotherapy;(2)ditherapy;(3)optional treatment with rarely used AEDs; and(4) treatment with multiple AEDs. Generic drugs were not permitted. Pharmacotherapy for seizures for both study groups was monitored by an independent panel of AED clinical pharmacology experts who were blinded to treatment assignment. Indirectness: No indirectness
Funding	Academic or government funding (This study was supported by the National Institutes of Health (grant numbers R21NS37897 and U01 NS42372).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: USUAL CARE versus SURGICAL INTERVENTION

Protocol outcome 1: Quality of life at 12-24 months at 12-24 months
- Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Quality of life using QOLIE-89 scale - overall scale at 24 months; Mean; Mean, Comments: Mean (95% CI)
9.9 (2.2 to 17.7)
;
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: UC/SURG: focal onset (82.6%/93.3%), simple partial (0/0), complex partial (3/2), secondary generalised (0/0) ; Group 1 Number missing: 5, Reason: 3 lost to follow up, 2 requested surgery; Group 2 Number missing: 1, Reason: 1 withdrew
- Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Quality of life using QOLIE-89 scale - cognitive scale at 24 months; Mean; , Comments: Mean (95% CI)
7.8 (0.9 to 14.7);
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: UC/SURG: focal onset (82.6%/93.3%), simple partial (0/0), complex partial (3/2),

Study	Engel 2012[19]
secondary generalised (0/0) ; Group 1 Number missing: 5, Reason: 3 lost to follow up, 2 requested surgery; Group 2 Number missing: 1, Reason: 1 withdrew Protocol outcome 2: First seizure at 12- 24 months at 12- 24 months - Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: First seizure at 24 months at 24 months; HR 0.259 (95% CI: 0.122-0.552) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: UC/SURG: focal onset (82.6%/93.3%), simple partial (0/0), complex partial (3/2), secondary generalised (0/0) ; Group 1 Number missing: 5, Reason: 3 lost to follow up, 2 requested surgery; Group 2 Number missing: 1, Reason: 1 withdrew Protocol outcome 3: Seizure frequency (50% or greater reduction in seizure frequency) at 12- 24 months at 12- 24 months - Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Seizure frequency at 24 months at 24 months; Group 1: mean 9.47 (SD 22.09); n=19, Group 2: mean 0.31 (SD 0.85); n=13 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: UC/SURG: focal onset (82.6%/93.3%), simple partial (0/0), complex partial (3/2), secondary generalised (0/0) ; Group 1 Number missing: 5, Reason: 3 lost to follow up, 2 requested surgery; Group 2 Number missing: 1, Reason: 1 withdrew Protocol outcome 4: Cognitive outcomes (including neuropsychological measures of global cognitive functioning, executive functioning and memory using a validated scale) at 12- 24 months at 12- 24 months - Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: RAVLT delayed recall (Rey Auditory Verbal Learning Test) at 24 months; Group 1: mean 0.6 (SD 2); n=23, Group 2: mean -1.5 (SD 3.6); n=15 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: UC/SURG: focal onset (82.6%/93.3%), simple partial (0/0), complex partial (3/2), secondary generalised (0/0) ; Group 1 Number missing: 5, Reason: 3 lost to follow up, 2 requested surgery; Group 2 Number missing: 1, Reason: 1 withdrew - Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Boston Naming Test at 24 months; Group 1: mean 0.8 (SD 4); n=23, Group 2: mean -3.4 (SD 7.7); n=15 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: UC/SURG: focal onset (82.6%/93.3%), simple partial (0/0), complex partial (3/2), secondary generalised (0/0) ; Group 1 Number missing: 5, Reason: 3 lost to follow up, 2 requested surgery; Group 2 Number missing: 1, Reason: 1 withdrew Protocol outcome 5: Adverse events (such as infection, stroke, severe bleeding) at N/A - Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Serious adverse events at 24 months; Group 1: 5/23, Group 2: 4/15 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: UC/SURG: focal onset (82.6%/93.3%), simple partial (0/0), complex partial (3/2), secondary

Study	Engel 2012[19]
generalised (0/0) ; Group 1 Number missing: 5, Reason: 3 lost to follow up, 2 requested surgery; Group 2 Number missing: 1, Reason: 1 withdrew	
Protocol outcomes not reported by the study	Quality of life at>24-60 months at >24-60 months; Mortality at 12-24 months at 12-24 months; Mortality at >24-60 months at >24-60 months; Seizure freedom (100% reduction in seizure frequency) at >24-60 months at >24-60 months; Seizure frequency (50% or greater reduction in seizure frequency) at >24-60 months at >24-60 months; Healthcare resource use at N/A; Social functioning (measures of adaptive functioning or adaptive behaviour using a validated scale) at 12- 24 months at 12- 24 months; Social functioning (measures of adaptive functioning or adaptive behaviour using a validated scale) at >24-60 months at >24-60 months; Cognitive outcomes (including neuropsychological measures of global cognitive functioning, executive functioning and memory using a validated scale) at >24-60 months at >24-60 months; In children and young people: neurodevelopmental outcomes (behavioural and emotional outcomes measured with a validated scale) at 12- 24 months at 12- 24 months; In children and young people: neurodevelopmental outcomes (behavioural and emotional outcomes measured with a validated scale) at >24-60 months at >24-60 months.

Study	Wiebe 2001[83]; Fiest,2014[21]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=80)
Countries and setting	Conducted in USA; Setting:
Line of therapy	2nd line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: EEG/MRI
Stratum	Children, young people and adults with confirmed pharmacoresistant epilepsy
Subgroup analysis within study	Not applicable

Study	Wiebe 2001[83]; Fiest,2014[21]
Inclusion criteria	At least 16 years old and to have had seizures with strong temporal-lobe semiology for more than one year, seizures had to have occurred monthly, on average, during the preceding year, despite the use of two or more anticonvulsant drugs, one of which was phenytoin, carbamazepine, or valproic acid
Exclusion criteria	Brain lesions that required urgent surgery and those with progressive central nervous system disorders, active psychosis, pseudo seizures, a full-scale IQ lower than 70, previous surgery for epilepsy, focal extratemporal spikes or slowing on scalp-recorded EEG, or evidence on MRI of extratemporal lesions capable of producing the patient's seizures or of bilateral and equally severe epileptogenic lesions in the temporal lobe
Age, gender and ethnicity	Age - Mean (SD): Medical group 34.4 (9.9), surgical group 35.5 (9.4) years. Gender (M:F): Medical group (%) 52.5/47.5, surgical group (%) 42.5/57.5. Ethnicity: Not stated
Further population details	1. Children and young people: Not applicable 2. Girls and women of who are able to get pregnant (including those who are pregnant and breastfeeding): Not applicable 3. Older people: Not applicable 4. People with learning disabilities: Not applicable 5. Type of epilepsy: Not applicable
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Surgical intervention. Temporal lobe epilepsy. Duration 12 months. Concurrent medication/care: Anti-epileptic medication. Indirectness: No indirectness (n=40) Intervention 2: Wait-list control. Wait-list control. Duration 12 months. Concurrent medication/care: Anti-epileptic medication. Indirectness: No indirectness
Funding	Academic or government funding (Physicians' Services Incorporated Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SURGICAL INTERVENTION versus WAIT-LIST CONTROL

Protocol outcome 1: Quality of life at 12-24 months at 12-24 months
- Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: QOLIE-89 at 12-24 months;
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Surgery vs wait-list control: history of status epilepticus -15.0% vs 12.5%, QOLIE-89 mean (SD) - 60.6 (15.3) vs 52.9 (19.2), MRI messial temporal sclerosis - 70.0% vs 72.5, MRI normal 15.0% vs 17.5&, number of epileptic drugs used before

Study	Wiebe 2001[83]; Fiest,2014[21]
randomisation median (range) - 6 (4-7) vs 6 (4-8) ; Group 1 Number missing: 4, Reason: One declined, 2 not eligible on EEC. MRI and neuro-psychological tests, 1 did not have seizures during investigations ; Group 2 Number missing: 0 - Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Adjusted odds of achieving MCID of benefit over 1 year period using QOLIE-89; Adjusted OR: 15.1 (95% CI: 2.7 – 84.8). Adjusted for gender, age and depression. The MCID is a clinically important *change* and so is not as affected by baseline imbalance as an absolute score would be. Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Surgery vs wait-list control: history of status epilepticus -15.0% vs 12.5%, QOLIE-89 mean (SD) - 60.6 (15.3) vs 52.9 (19.2), MRI messial temporal sclerosis - 70.0% vs 72.5, MRI normal 15.0% vs 17.5&, number of epileptic drugs used before randomisation median (range) - 6 (4-7) vs 6 (4-8) ; Group 1 Number missing: 4, Reason: One declined, 2 not eligible on EEC. MRI and neuro-psychological tests, 1 did not have seizures during investigations ; Group 2 Number missing: 0 - Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Adjusted odds of achieving MCID of benefit over 1 year period using QOLIE-31; Adjusted OR: 15.2 (95% CI: 2.6 – 88.0). Adjusted for gender, age and depression. The MCID is a clinically important *change* and so is not as affected by baseline imbalance as an absolute score would be. Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Surgery vs wait-list control: history of status epilepticus -15.0% vs 12.5%, QOLIE-31 mean (SD) – 86.6.6 (33.7) vs 77.4 (31.9), MRI messial temporal sclerosis - 70.0% vs 72.5, MRI normal 15.0% vs 17.5&, number of epileptic drugs used before randomisation median (range) - 6 (4-7) vs 6 (4-8) ; Group 1 Number missing: 4, Reason: One declined, 2 not eligible on EEC. MRI and neuro-psychological tests, 1 did not have seizures during investigations ; Group 2 Number missing: 0 - Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Adjusted odds of achieving MCID of benefit over 1 year period using HUI-111; Adjusted OR: 6.0 (95% CI: 1.7 – 21.5). Adjusted for gender, age and depression. The MCID is a clinically important *change* and so is not as affected by baseline imbalance as an absolute score would be. Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Surgery vs wait-list control: history of status epilepticus -15.0% vs 12.5%, HUI 111 mean (SD) – 0.62 (0.25) vs 0.52 (0.32), MRI messial temporal sclerosis - 70.0% vs 72.5, MRI normal 15.0% vs 17.5&, number of epileptic drugs used before randomisation median (range) - 6 (4-7) vs 6 (4-8) ; Group 1 Number missing: 4, Reason: One declined, 2 not eligible on EEC. MRI and neuro-psychological tests, 1 did not have seizures during investigations ; Group 2 Number missing: 0 - Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Adjusted odds of achieving MCID of benefit over 1 year	

Study	Wiebe 2001[83]; Fiest,2014[21]
period using SF-36 - PCS; Adjusted OR: 2.4 (95% CI: 1.0 – 5.8). Adjusted for gender, age and depression. The MCID is a clinically important *change* and so is not as affected by baseline imbalance as an absolute score would be. Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Surgery vs wait-list control: history of status epilepticus -15.0% vs 12.5%, SF-36 - PCS mean (SD) – 54.1 (13.9) vs 48.1 (15.2), MRI messial temporal sclerosis - 70.0% vs 72.5, MRI normal 15.0% vs 17.5&, number of epileptic drugs used before randomisation median (range) - 6 (4-7) vs 6 (4-8) ; Group 1 Number missing: 4, Reason: One declined, 2 not eligible on EEC. MRI and neuro-psychological tests, 1 did not have seizures during investigations ; Group 2 Number missing: 0	
- Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Adjusted odds of achieving MCID of benefit over 1 year period using SF-36 - MCS; Adjusted OR: 2.5 (95% CI: 1.0 – 6.6). Adjusted for gender, age and depression. Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Surgery vs wait-list control: history of status epilepticus -15.0% vs 12.5%, SF-36 - MCS mean (SD) - 46.2 (9.5) vs 39.3 (10.9), MRI messial temporal sclerosis - 70.0% vs 72.5, MRI normal 15.0% vs 17.5&, number of epileptic drugs used before randomisation median (range) - 6 (4-7) vs 6 (4-8) ; Group 1 Number missing: 4, Reason: One declined, 2 not eligible on EEC. MRI and neuro-psychological tests, 1 did not have seizures during investigations ; Group 2 Number missing: 0	
Protocol outcome 2: Mortality at 12-24 months at 12-24 months - Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Mortality at 12-24 months; Group 1: 0/36, Group 2: 1/40 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Surgery vs wait-list control: history of status epilepticus -15.0% vs 12.5%, QOLIE-89 mean (SD) - 60.6 (15.3) vs 52.9 (19.2), MRI messial temporal sclerosis - 70.0% vs 72.5, MRI normal 15.0% vs 17.5&, number of epileptic drugs used before randomisation median (range) - 6 (4-7) vs 6 (4-8) ; Group 1 Number missing: 4, Reason: One declined, 2 not eligible on EEC. MRI and neuro-psychological tests, 1 did not have seizures during investigations ; Group 2 Number missing: 0	
Protocol outcome 3: First seizure at 12- 24 months at 12- 24 months - Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: First seizure at 12-24 months; HR: 0.307 (95% CI:0.178-0.530) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Surgery vs wait-list control: history of status epilepticus -15.0% vs 12.5%, QOLIE-89 mean (SD) - 60.6 (15.3) vs 52.9 (19.2), MRI messial temporal sclerosis - 70.0% vs 72.5, MRI normal 15.0% vs 17.5&, number of epileptic drugs used before randomisation median (range) - 6 (4-7) vs 6 (4-8) ; Group 1 Number missing: 4, Reason: One declined, 2 not eligible on EEC. MRI and neuro- psychological	

Study	Wiebe 2001[83]; Fiest,2014[21]
tests, 1 did not have seizures during investigations ; Group 2 Number missing: 0 Protocol outcome 4: Adverse events (such as infection, stroke, severe bleeding) at N/A - Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Adverse events at 12-24 months; Group 1: 4/36, Group 2: 0/40 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Surgery vs wait-list control: history of status epilepticus -15.0% vs 12.5%, QOLIE-89 mean (SD) - 60.6 (15.3) vs 52.9 (19.2), MRI messial temporal sclerosis - 70.0% vs 72.5, MRI normal 15.0% vs 17.5&, number of epileptic drugs used before randomisation median (range) - 6 (4-7) vs 6 (4-8) ; Group 1 Number missing: 4, Reason: One declined, 2 not eligible on EEC. MRI and neuro-psychological tests, 1 did not have seizures during investigations ; Group 2 Number missing: 0 - Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Adverse events at 12-24 months; Risk of bias: All domain - ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at>24-60 months at >24-60 months; Mortality at >24-60 months at >24-60 months; Seizure freedom (100% reduction in seizure frequency) at >24-60 months at >24-60 months; Seizure frequency (50% or greater reduction in seizure frequency) at 12- 24 months at 12- 24 months; Seizure frequency (50% or greater reduction in seizure frequency) at >24-60 months at >24-60 months; Healthcare resource use at N/A; Social functioning (measures of adaptive functioning or adaptive behaviour using a validated scale) at 12- 24 months at 12- 24 months; Social functioning (measures of adaptive functioning or adaptive behaviour using a validated scale) at >24-60 months at >24-60 months; Cognitive outcomes (including neuropsychological measures of global cognitive functioning, executive functioning and memory using a validated scale) at 12- 24 months at 12- 24 months; Cognitive outcomes (including neuropsychological measures of global cognitive functioning, executive functioning and memory using a validated scale) at >24-60 months at >24-60 months; In children and young people: neurodevelopmental outcomes (behavioural and emotional outcomes measured with a validated scale) at 12- 24 months at 12- 24 months; In children and young people: neurodevelopmental outcomes (behavioural and emotional outcomes measured with a validated scale) at >24-60 months at >24-60 months.

Appendix I Forest plots

I.1 Surgery versus waitlist-control/medical treatment

Figure 5: Mortality at 1 year

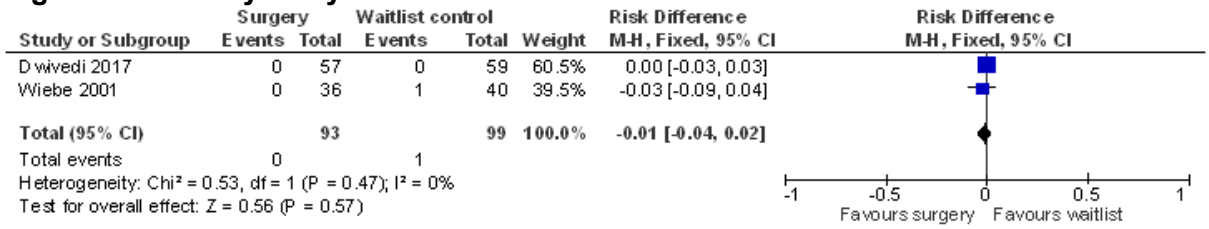


Figure 6: Quality of life at 1-2 years (Paediatric QoL inventory scale, QOLIE-89 scale, 0 to 100 scale, high is good outcome)

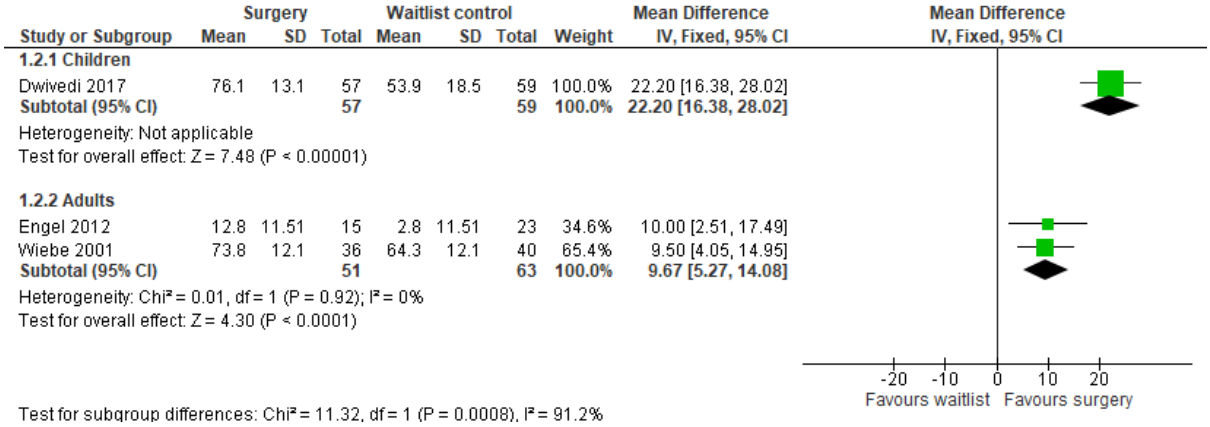


Figure 7: Quality of life at 2 years (QOLIE-89 cognitive scale, change score, 0 to 100 scale, high is good outcome)

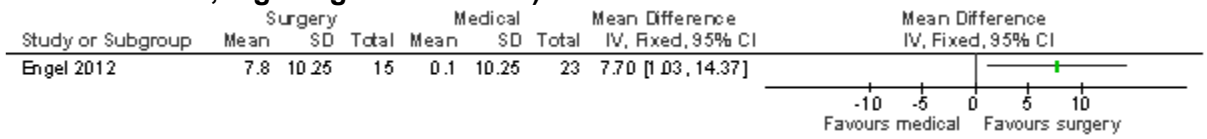


Figure 8: Quality of life: adjusted OR for achieving clinically significant benefit in QOLIE-89 score within 1 year

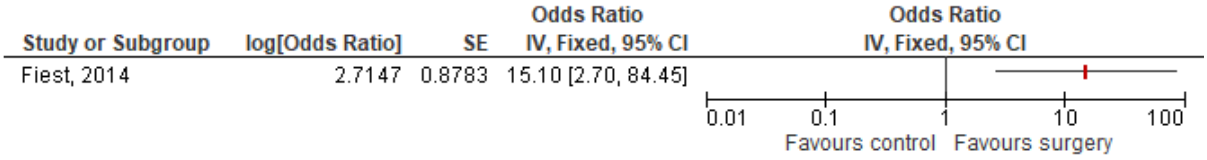


Figure 9: Quality of life: adjusted OR for achieving clinically significant benefit in QOLIE-31 score within 1 year

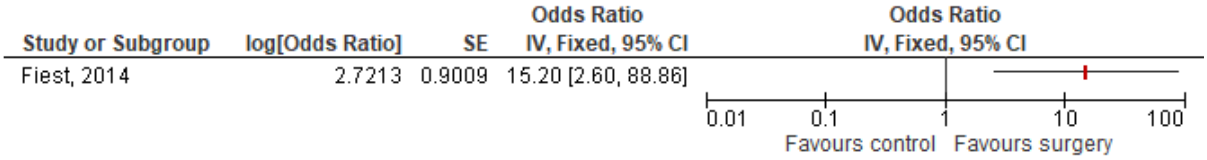


Figure 10: Quality of life: adjusted OR for achieving clinically significant benefit in HUI 111 score within 1 year

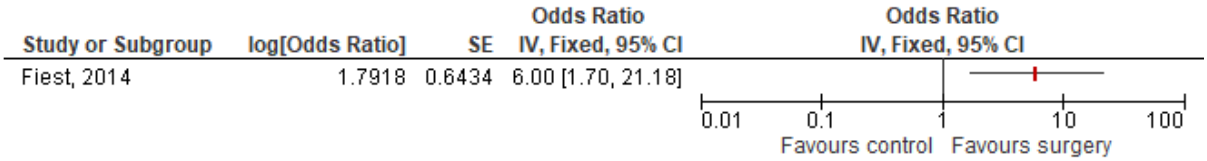


Figure 11: Quality of life: adjusted OR for achieving clinically significant benefit in SF-36 PCS score within 1 year

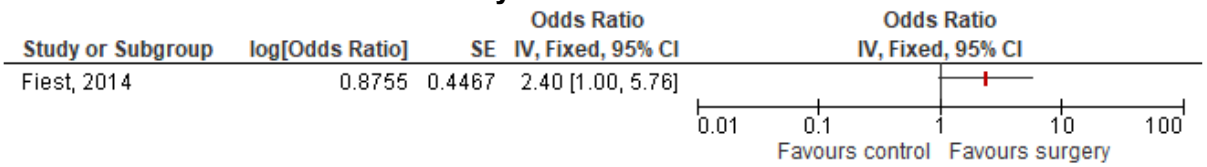


Figure 12: Quality of life: adjusted OR for achieving clinically significant benefit in SF-36 MCS score within 1 year

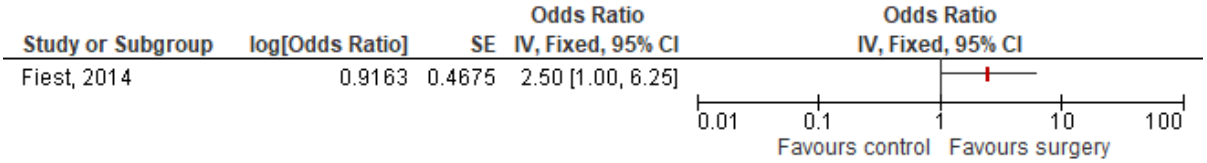


Figure 13: Seizure freedom at 1 year

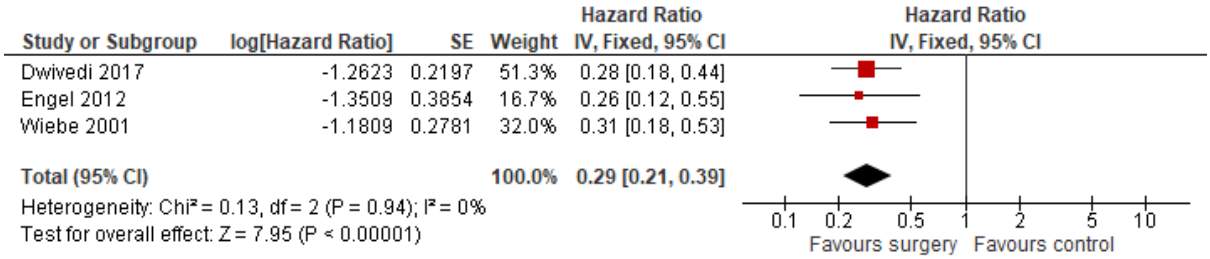


Figure 14: Seizure freedom in second year of follow up (months 12 - 24 after intervention)

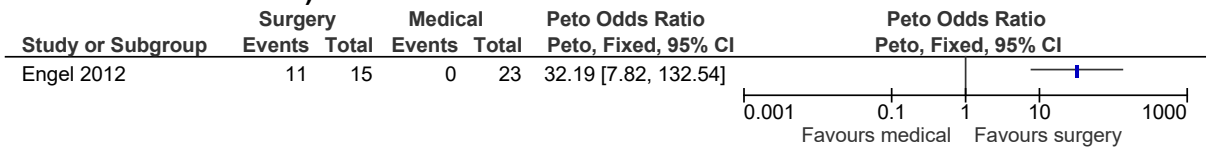


Figure 15: Seizure frequency at 22 to 24 months

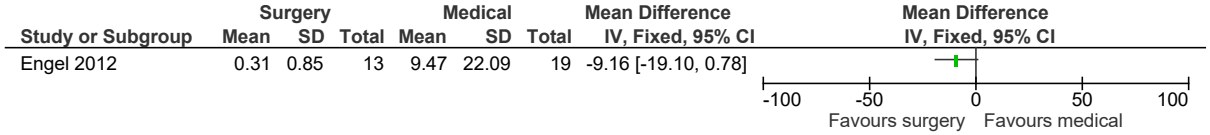


Figure 16: Cognitive outcomes at 1 year (Binet-Kamat test, high is good outcome)

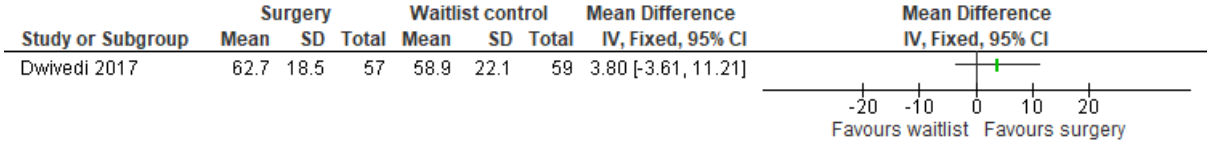


Figure 17: Cognitive outcomes at 2 years (Boston Naming Test, change score, high is good outcome)

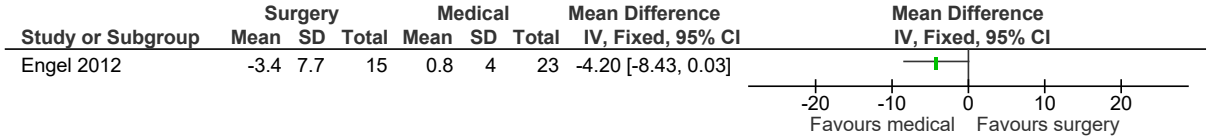


Figure 18: Cognitive outcomes at 2 years (RAVLT delayed recall, change score, high is good outcome)

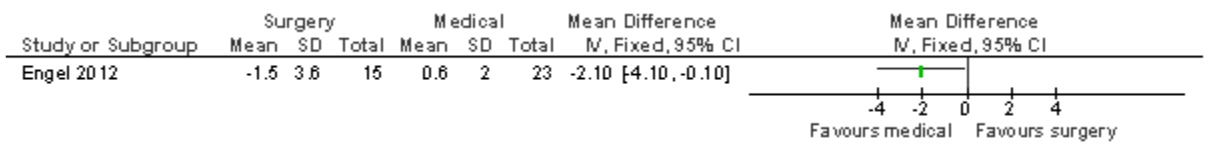


Figure 19: Social functioning (Child behaviour Checklist, 0 to 100, high is poor outcome)

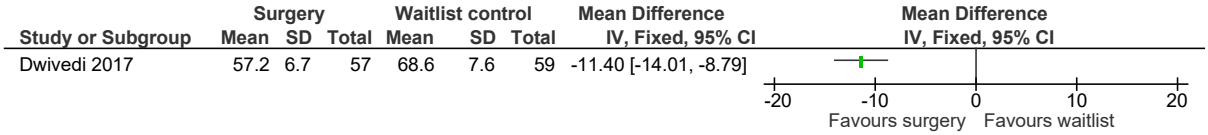


Figure 20: Serious adverse events at 1-2 years

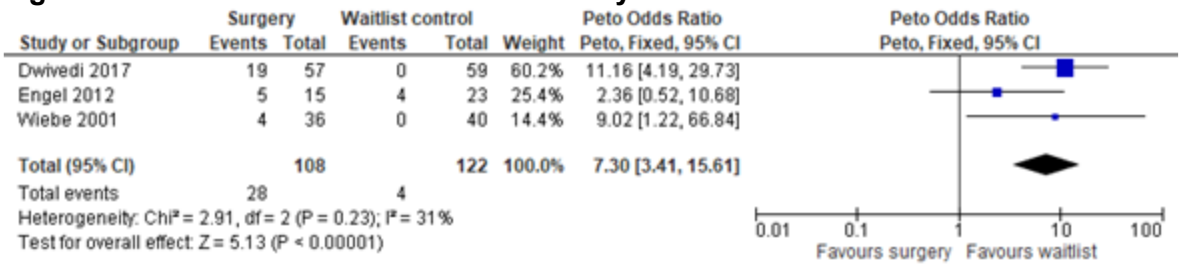
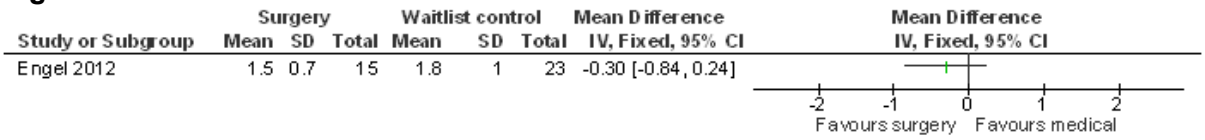


Figure 21: Number of AEDs used



Appendix J GRADE tables

Table 17: Clinical evidence profile: surgery versus waitlist-control/medical treatment

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery	Waitlist-Control	Relative (95% CI)	Absolute		
Mortality (follow-up 1 years)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/93 (0%)	1/99 (1%)	RD -0.01 (-0.04 to 0.02)	10 fewer per 1000 (from 40 fewer to 20 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Quality of life - Children (follow-up 1 year; measured with: Paediatric QoL inventory scale; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	57	59	-	MD 22.2 higher (16.38 to 28.02 higher)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life - Adults (follow-up 1-2 years; measured with: QOLIE-89 scale; range of scores: 0-100; Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	51	63	-	MD 9.67 higher (5.27 to 14.08 higher)	⊕⊕OO LOW	CRITICAL
Quality of life (change score) (follow-up 2 years; measured with: QOLIE-89 cognitive scale; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15	23	-	MD 7.7 higher (1.03 to 14.37 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (follow up 1 year; measured with QOLIE-89 overall scale – adjusted odds of achieving clinically significant benefit over 1 year period												
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	36	40	OR: 15.1 (95% CI 2.7 – 84.8)	-	⊕⊕⊕O MODERATE	CRITICAL
Quality of life (follow up 1 year; measured with QOLIE-31 overall scale – adjusted odds of achieving clinically significant benefit over 1 year period												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	36	40	OR: 15.2 (95% CI 2.6 – 88.0)	-	⊕⊕⊕O MODERATE	CRITICAL
Quality of life (follow up 1 year; measured with HUI-111 overall scale – adjusted odds of achieving clinically significant benefit over 1 year period												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	36	40	OR: 6.0 (95% CI 1.7 – 21.5)	-	⊕⊕⊕O MODERATE	CRITICAL
Quality of life (follow up 1 year; measured with SF-36 PCS overall scale – adjusted odds of achieving clinically significant benefit over 1 year period												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	36	40	OR: 2.4 (95% CI 1.0 – 5.8)	-	⊕⊕OO LOW	CRITICAL
Quality of life (follow up 1 year; measured with SF-36 MCS overall scale – adjusted odds of achieving clinically significant benefit over 1 year period												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	36	40	OR: 2.5 (95% CI 1.0 – 6.6)	-	⊕⊕OO LOW	CRITICAL
Seizure freedom (follow-up 1 years); HR for first seizure*												
3	randomised trials	No serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	57	59	HR 0.29 (0.21 to 0.39)	-	⊕⊕⊕⊕ HIGH	CRITICAL
Seizure freedom in second year of follow up (follow-up 12-24 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	11/15 (73.3%)	0/23 (0%)	Peto OR 32.19 (7.82 to 132.54)	730 more per 1000 (from 510 more to 960 more)	⊕⊕⊕O MODERATE	CRITICAL
Seizure frequency at 22 to 24 months (follow-up 2 years; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	13	19	-	MD 9.16 lower (19.1 lower to 0.78 higher)	⊕⊕OO LOW	CRITICAL
Cognitive outcomes (follow-up 1 years; measured with: Binet-Kamat test; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	57	59	-	MD 3.8 higher (3.61 lower to 11.21 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Cognitive outcomes (change score) (follow-up 2 years; measured with: Boston Naming Test; Better indicated by lower values)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15	23	-	MD 4.2 lower (8.43 lower to 0.03 higher)	⊕⊕OO LOW	IMPORTANT
Cognitive outcomes (change score) (follow-up 2 years; measured with: RAVLT delayed recall; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15	23	-	MD 2.1 lower (4.1 to 0.1 lower)	⊕⊕OO LOW	IMPORTANT
Social functioning (follow-up 1 years; measured with: Child behaviour Checklist; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	57	59	-	MD 11.4 lower (14.01 to 8.79 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Serious adverse events (follow-up 1 years)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	28/108 (25.9%)	4/122 (3.3%)	Peto OR 7.30 (3.41 to 15.61)	230 more per 1000 (from 140 more to 320 more)	⊕⊕⊕O MODERATE	IMPORTANT
Number of AEDs used (follow-up 2 years; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15	23	-	MD 0.30 lower (0.84 lower to 0.24 higher)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 increment if I^2 >50% and <75% or by 2 increments if I^2 =75% or higher.
[4] None of the sub-grouping strategies resolved heterogeneity, so a random effects model was used
*Hazard is for first seizure, so a lower hazard represents a benefit; thus, a HR <1 indicates a benefit for surgery

Appendix K Economic evidence tables

Study	Burch 2012 [10] & Hinde 2014 [23]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA **Study design:** Probabilistic decision analytic model **Approach to analysis:** 1 year decision tree that captures the tests and 1-year outcomes following the interventions (surgery or medical management). Includes complications (transient or permanent) and its QoL impact. At the end of the short term model, you could either; be having disabling seizures, achieved seizure freedom, or have died. These are the states that a patient can enter the Markov model in. The Markov model also has an additional 3 tunnel states to track how long people are SF (SF for 1 year, SF for 2 years, SF for > 2 years (on or off AEDs).	**Population:** Medically refractory epileptic patients with TLE who have had discordant findings from initial video-EEG and MRI scans. Patients deemed eligible for a presurgical evaluation are defined as medically refractory (failure to respond to at least two antiepileptic drugs). **Cohort settings:** Start age: 35 Male: 49% **Intervention 1:** Medical Management (MM) **Intervention 2:** FDG-PET • If positive, patients offered surgery. • If negative, patients offered MM • If uncertain, patients offered MM	**Total costs (mean per patient):** Intervention 1: £23,783 Intervention 2: £26,637 Intervention 3: £27,710 Incremental (2-1): £2,845 Incremental (3−2): £1,074 **Currency & cost year:** 2010 UK pounds **Cost components incorporated:** Cost of tests – FDG-PET & iEEG. Surgery costs, surgery complication costs, annual cost of AEDs, non-drug costs for SF and	**QALYs (mean per patient):** Intervention 1: 12.88 Intervention 2: 14.59 Intervention 3: 14.92 Incremental (2-1): 1.71 Incremental (3-2): 0.34	**ICER (Intervention 2 versus Intervention 1):** £1,671 per QALY gained (pa) Probability Intervention 2 cost effective (£20K/30K threshold): 3%/3% **ICER (Intervention 3 versus Intervention 2):** £3,201 per QALY gained (pa) Probability Intervention 3 cost effective (£20K/30K threshold): 83%/84% **Analysis of uncertainty:** Scenario analysis conducted assuming long-term outcomes for patients were the same as MM. This results in Intervention 2 becoming the most cost-effective strategy (ICER 2, £11.526; ICER 3, £32,876). Probability Intervention 2 cost effective (£20K/30K threshold): 37%/36% Probability Intervention 3 cost effective (£20K/30K threshold): 27%/39% PSA indicated, disutility of DS for MM and surgery (no complications) had the potential to alter results; but strategy 3 was still the

Perspective: UK NHS **Time horizon:** lifetime **Treatment effect duration:**[(a)] lifetime **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**Intervention 3:** FDG-PET • If positive, patients offered surgery • If negative, patients offered MM • If uncertain, patients offered iEEG to determine treatment (positive iEEG leads to surgery and negative or uncertain iEEG results in MM)	seizure-persistent patients.		most cost effective in most cases (0.85 and 0.93 respectively). The results became more sensitive to the short-term effectiveness of surgery, whereby if the success rates of surgery is < 55% MM would be the most cost-effective strategy. The base case assumed compliance to iEEG, and surgery was 100%. Results from the base case and scenario analysis would not be altered unless compliance was < 20%.

Data sources

Health outcomes: The model is structured in terms of the strategies evaluated is based on Uijl et al [74]. The structure of the Markov model is based on the model by Choi et al [14] - a decision analysis modelling health outcomes. The decision tree was assumed to be 1 year to be consistent with Choi et al's [14] study. Mortality due to an invasive procedure is assumed to be the same for iEEG and surgery. Outcomes: One-year seizure outcomes after temporal lobe resection estimate pooled from 13 studies (including 1 RCT which is included in our clinical review). Probability of seizure freedom for MM arm after one year sourced from the RCT. Long-term seizure outcomes from temporal lobe resection - seizure relapse and the probability of becoming seizure free between 1 and 5 year sourced from 5 observational studies. The probability of becoming seizure after five years sourced from 2 observational studies. Long-term seizure outcomes after MM sourced from study of patients with intractable epilepsy (50% of patients with TLE). Surgical morbidity and surgical mortality sourced from the AAN systematic review (1 RCT and 24 observational studies). Mortality from epilepsy of patients who have undergone resections soured from 2 observational studies. For the MM arm data was pooled for people with intractable epilepsy.

Quality-of-life weights: HRQoL for the general population sourced and based off the EQ-5D. Decrements sourced from Choi et al, which used standard gamble from patients who had undergone temporal lobe resections, were applied to the general population weights.

Cost sources: Cost of tests, surgery, and surgery complications; NHS reference costs 2009-10. Annual cost of AEDs (average costs) and non-drug costs; NICE guidelines: 2011 epilepsies partial update [37].

Comments

Source of funding: National Institute for Health Research (NIHR).

Limitations: A mix of RCTs and observational studies are used to populate model parameters. Some simplifying assumptions are made due to lack of evidence available. In some instances, it is not apparent what timeframe is being analysed in evidence drawn from the wider literature used to inform model parameters. Strategies included may not reflect current practice of the diagnostic test pathway.

Overall applicability:[(b)] Partially applicable **Overall quality:**[(c)] Minor Limitations

Abbreviations: AAN= American Academy of Neurology; AEDs= Antiepileptic drugs; CUA= cost–utility analysis; DS= disabling seizure; EEG= electroencephalography; FDG-PET= fluorodeoxyglucose positron emission tomography; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); iEEG=

invasive/intracranial electroencephalography; MM= medical management; MRI= magnetic resonance imaging; ICER= incremental cost-effectiveness ratio; pa= probabilistic analysis; QALYs= quality-adjusted life years; QoL= quality of life; SF= seizure free; TLE= temporal lobe epilepsy

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**Kovacs 2021[29]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA **Study design:** Probabilistic decision analytic model **Approach to analysis:** The decision tree model (1 year) captures short-term clinical outcomes associated with iEEG localization strategy and considers three treatment endpoints: (1) patients continue to receive MM independently (unsuccessful localization of EZ or multiple epileptic foci, or the EZ exists near or inside an eloquent brain region); (2) patients are referred for surgery and survive the procedure; and (3) patients die as a result of iEEG intervention or resective surgery. For those who survive initial iEEG intervention and the	**Population:** Adults with drug-resistant, partial-onset epilepsy. Assumed that compliance to iEEG intervention and epilepsy surgery is 100%. **Cohort settings:** Start age: 35 Male: NR, states it was assumed to be the same as the Hungarian general population **Intervention 1:** Medical Management (MM) **Intervention 2:** Intracranial EEG (iEEG) monitoring: placement of subdural grid electrodes (SDGs) **Intervention 3:** iEEG monitoring: stereotactic implantation of depth electrodes (stereoelectroencephalography or SEEG).	**Total costs (mean per patient):** Intervention 1: £13,624 Intervention 2: £23,271 Intervention 3: £30,461 Incremental (2-1): £9,647 Incremental (3−2): £16,837 **Currency & cost year:** 2019 Euros (presented here as 2019 UK pounds[(b)]) **Cost components incorporated:** Cost of iEEGs and surgery:	**QALYs (mean per patient):** Intervention 1: 8.304 Intervention 2: 11.748 Intervention 3: 12.235 Incremental (2-1): 3.444 Incremental (3-2): 3.931	**ICER (Intervention 2 versus Intervention 1):** £2,802 per QALY gained (pa) Probability Intervention 2 cost effective (£38K threshold): 99.7% **ICER (Intervention 3 versus Intervention 2):** £4,284 per QALY gained (pa) Probability Intervention 3 cost effective (£38K threshold): 99.5% **Analysis of uncertainty:** One-way sensitivity and scenario analyses undertaken. None of these deterministic sensitivity analyses lead to a substantial change in ICER or resulted in an ICER over £38K. The scenario analyses undertaken set the parameter values to extreme values. Of these it was the elimination of utility difference between DS and SF health states that had the greatest impact on the ICERs of surgery versus MM. The ICERs remained

subsequent surgery, there are three possible outcomes: (1) achieving SF for at least one year, (2) having a disabling seizures (DS) within this year, or (3) dying within this year due to epilepsy-related mortality. Patients enter the long-term Markov model directly from the short-term model, there are three health states seizure-free, DS and death. **Perspective:** Hungarian healthcare payer **Time horizon:** 30 years **Treatment effect duration:**[(a)] lifetime / 30 years **Discounting:** Costs: 3.7%; Outcomes: 3.7%	For both interventions 2 and 3: - if successful epileptogenic zone localisation, patients offered surgery (temporal or extratemporal resective surgery). - if unsuccessful patients offered MM.	- Admission and preimplantation - Implantation (with the cost of electrodes) - Monitoring - Desimplantation - Discharge - Resective surgery Cost of SAEs and medication costs also included. Medication costs reduced based on Engel classification and whether or not they had surgery.		below £20K, therefore did not impact the conclusions of the model.
Data sources				
Health outcomes: Surgical efficacy was defined and measured as the probability of an Engel Class I outcome in the overall patient group in both the short- and long-term models (Cohen Gadol 2006, MadDougall 2009). Short term outcomes for iEEG taken from multiple studies: Hotan 2016, Devaux 2008, Mullin 2016, Hedegard 2014. The structure of the Markov model is based on the model by Burch 2012[10] (reported above). To populate the short- and long-term models with effectiveness data, the authors conducted a targeted literature review and applied the results of those publications bearing at least a 5-year follow-up and a higher number of patients in the sample, although not stated it appears most studies used for data inputs were non-RCT. Baseline characteristics including general population mortality were based on Hungarian observational data. SMRs taken from Choi 2008[14]. MM arm data taken from Choi 2008[14], which in turn used one of the RCTs included in the clinical review: Wiebe 2001[19]. **Quality-of-life weights:** Utility values applied in the model were estimated by implementing a multilevel regression analysis developed by de Kinderen 2016 which provided a utility function for transforming clinically relevant epilepsy outcome measures into utility estimates. Health states, based on clinically				

important epilepsy attributes (e.g., seizure frequency, seizure severity, side-effects), were valued by a sample of the Dutch population (N = 525) based on the time trade-off method.

Cost sources: Unit costs and resource use taken from a Hungarian neurosurgical department (University of Pecs). Short and long-term medication costs for AED treatment taken from data provided by the National Institute of Clinical Neurosciences in Budapest. Probability of SAE taken from the literature. Of note all costs were originally calculated in Hungarian forints (HUF) and converted into euros (€).

Comments

Source of funding: European Union and Hungarian Government.

Limitations: Study evaluates the cost effectiveness of different diagnostic strategies for potential patients undergoing temporal or extratemporal resective surgery. The diagnostic testing strategies used to identify eligible patients may not reflect those used in current practice. Non-UK perspective may not reflect current UK NHS practice. EQ-5D not used for QoL. Unclear if literature used to inform model parameters were appropriate for this subset of patients who would undergo iEEG diagnostic procedures prior to surgery. Treatment effects based on a mix of RCTs and observational data. Not all data sources clearly reported.

Overall applicability:[(c)] Partially applicable **Overall quality:**[(d)] Minor limitations

Abbreviations: AEDs= Antiepileptic drugs; CUA= cost–utility analysis; DS= disabling seizure; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); iEEG= invasive/intracranial electroencephalography; ICER= incremental cost-effectiveness ratio; pa= probabilistic analysis; QALYs= quality-adjusted life years; MM= medical management; QoL= quality of life; SAE= serious adverse events; SDGs= subdural grid electrodes; SEEG= stereoelectroencephalography; SF= seizure free.

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Converted using 2019 purchasing power parities[47]

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix L Health economic model

An original cost-utility analysis was developed, assessing the cost-effectiveness of resective epilepsy surgery in adults with drug refectory epilepsy. Original health economic modelling was also planned to model the cost-effectiveness of resective epilepsy surgery in children, but insufficient data were available to model for this population. Full details of the health economic analysis can be found in the Economic analysis report.

The committee identified this as a high priority area as they thought there could be a reluctance to refer people for resective epilepsy surgery. The committee wanted to demonstrate benefits of resective epilepsy in terms of improved seizure freedom and long-term cost savings.

The model can be found in the supplementary data submitted with the guideline.