National Institute for Health and Care Excellence

FINAL

Epilepsies in children, young people and adults

Cost-utility analysis: The cost effectiveness of resective epilepsy surgery in adults

NICE guideline NG217

Economic analysis report

April 2022

FINAL

Developed by the National Guideline Centre

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1 Methods

1.1 Model overview

A cost-utility analysis was undertaken where lifetime quality-adjusted life years (QALYs) and costs from a current UK NHS and personal social services perspective were considered. The analysis followed the standard assumptions of the NICE reference case for interventions with health outcomes in an NHS setting, including discounting at 3.5% for costs and health effects.[23] An incremental analysis was undertaken.

1.1.1 Comparators

The following comparators were included in the analysis:

1. Resective epilepsy surgery
2. Medical management

In clinical practice there are a number of different types of resective epilepsy surgery people can receive. However, in adults, the most common type is temporal lobe resection. The committee wanted to incorporate all types of epilepsy surgery in this cost effectiveness analysis so conclusions could be made regarding the cost effectiveness of epilepsy surgery in general. The RCTs included in the clinical review which were used to inform the short-term outcomes of our health economic model assessed the effectiveness of temporal lobe resection. The long-term effectiveness data for epilepsy surgery was taken from de Tisi 2011[11]. In that study, 81% of people received anterior temporal lobe resection, 7% of people received a temporal lesionectomy, 3% of people received extratemporal lesionectomy, 3% of people received extratemporal lobe resection, 2% of people received a hemispherectomy, and 1% of people received epilepsy surgical resection as part of palliative care. The committee noted that the proportion of people undergoing each type of surgical procedure was reflective of what was observed in UK clinical practice. However, the cost effectiveness of each specific type of surgical procedure, is not estimable from this model because the model parameters (seizure outcomes, utilities, and costs) are not well defined for specific procedures. Furthermore, the type of surgical procedure that will be suitable will only be apparent after preoperative assessment has taken place. Given the magnitude of the cost of assessment, it is appropriate to evaluate surgery in general, at the point of referral for assessment.

1.1.2 Population

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

Original health economic modelling was planned to model the cost effectiveness of epilepsy surgery in both adults and children. However, insufficient data were available to model the cost effectiveness of epilepsy surgery in children. In particular, there was a lack of data on health state utilities, epilepsy mortality and longer-term seizure freedom outcomes in children. The committee therefore agreed that the cost effectiveness of epilepsy surgery in children could be determined based on the results of the adult cost effectiveness analysis in conjunction with qualitative judgements being made about how the results may differ in a paediatric population.

1.2 Approach to modelling

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 long-term outcomes and costs.

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The one-year decision tree model reflects the immediate period following the intervention and the cost of pre-surgical evaluation. Treatment effectiveness data came from the clinical effectiveness review.

Further details on the decision tree model can be found in section 1.2.1.

The decision tree model only captures immediate consequences of the intervention as reported by the randomised trials, which was seizure freedom at 1 year [13, 44] and for one trial 2 years [13]. In order to estimate costs and outcomes beyond the period of 1 year, a Markov model was developed for each comparator using data from two long-term outcome studies:

- One long-term study reported outcomes for people after epilepsy surgery[11] and
- an additional long-term study reported outcomes for people with drug-refractory epilepsy receiving medical management[8].

People start in the decision tree and then move to the Markov model at the end of the 1-year time period entering the corresponding Markov state determined by the final state of the decision tree model. They then pass through a Markov model of 49 cycles of 1 year each. Time spent in each health state was calculated to determine costs and QALYs associated with each intervention. The comparison between the mean results of each intervention allowed us to identify the most cost-effective strategy. More details on the Markov model structure are described in section 1.2.1. To account for uncertainty, a probabilistic analysis was undertaken (see section 1.2.2 for further details).

1.2.1 Model structure

The decision tree is a two-arm decision tree comparing resective epilepsy surgery and medical management. After resective epilepsy surgery or continued medical management people can either have remaining seizures or be seizure free and at the end of the one-year period people can be either alive or dead. Costs and utilities were applied to each health state (seizure-free and not seizure-free) and the cost associated with assessment for resective epilepsy surgery and surgery, were included in the surgery arm.

The cost for people undergoing assessment for resective epilepsy but not receiving surgery was also included in the model to capture the total cost of assessment for resective epilepsy surgery. As part of assessment for resective epilepsy people are either identified as, being an eligible surgery candidate or not being an eligible surgery candidate. In addition, of those people who are identified as eligible surgery candidate a proportion of people may chose not to proceed with resective epilepsy surgery. Omitting the costs of preoperative assessment for those people who are not eligible for resective epilepsy surgery or decide not to proceed with resective epilepsy surgery would therefore be underestimating the total costs of referring people for resective epilepsy surgery. People receiving resective epilepsy surgery also had a probability of experiencing long-term complications from surgery (for example, stroke or a visual field defect). Costs and a utility decrement associated with long-term complications were also applied to the model.

The structure of the decision tree can be found in Figure 1.

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Figure 1: Model structure – decision tree

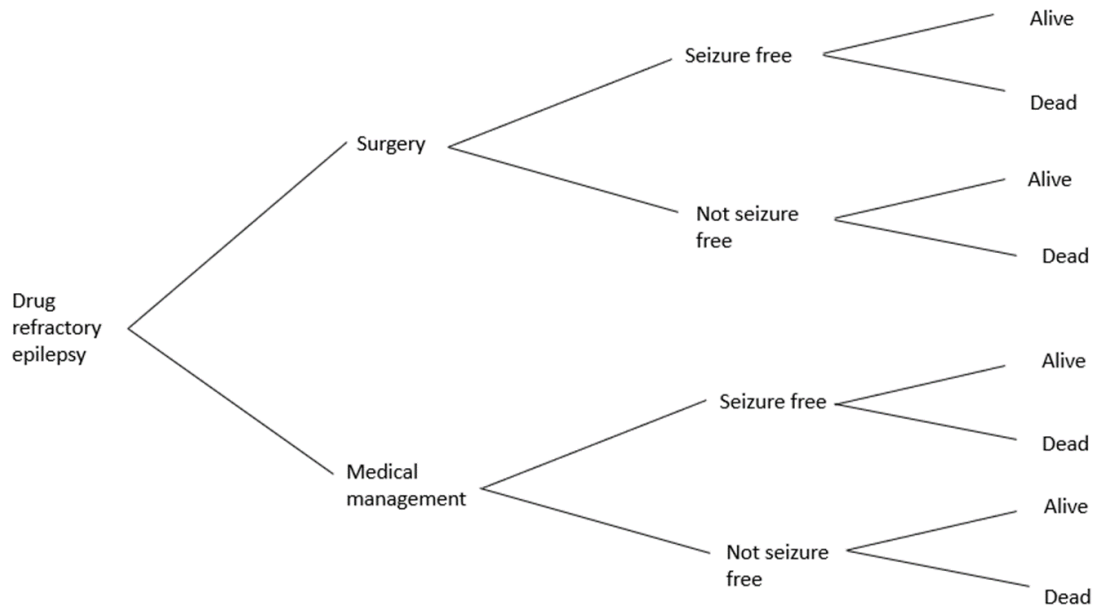

Figure 2 represents the long-term structure of the model. After one-year, patients enter into the Markov model in the health state they finished in the decision tree. For both resective epilepsy surgery and continued medical management, patients can enter the Markov model, being seizure free, having remaining seizures, or having died. The Markov model consists of 6 health states. The arrows in the Markov model represent a probability associated with transitioning to a health state or remaining in a given state.

The Markov model has four tunnel states, seizure free for one year, seizure free for two years, seizure free for three or more years, and seizure free and off Anti-Seizure Medications (ASMs). Tunnel states add memory into the Markov model relaxing the Markovian assumption. In the four tunnel states patients have an annual probability of relapsing and dying in addition to annual probability of moving to the next tunnel state.

Patients exiting the decision tree in the seizure free health state enter the Markov model in the ‘seizure free – 1 year’ health state. These seizure free patients then have an annual probability of transitioning to the tunnel state ‘seizure free – 2 years’. Patients transitioning to the ‘seizure free – 2 years’ health state then have an annual probability of transitioning to ‘seizure free – 3 years +’. For patients who transition to the ‘seizure free – 3 years +’, these people can remain seizure free, and so remain in this health sate, or transition to the seizure free and off ASMs health state. If people transition to the seizure free and off ASMs health state and remain in this health state it is assumed they remain seizure free and off their ASMs until they transition to the not seizure free or dead health state (i.e., people cannot recommence treatment with ASMs unless they transition to the not seizure free health state).

People entering the Markov model in the not seizure free health state or transitioning to this health state throughout the lifetime horizon of this model have a probability of remaining in this health state, transitioning to the seizure free for one year health state or dying.

By definition, patients who transition to the dead state have a 100% probability of remaining in this state.

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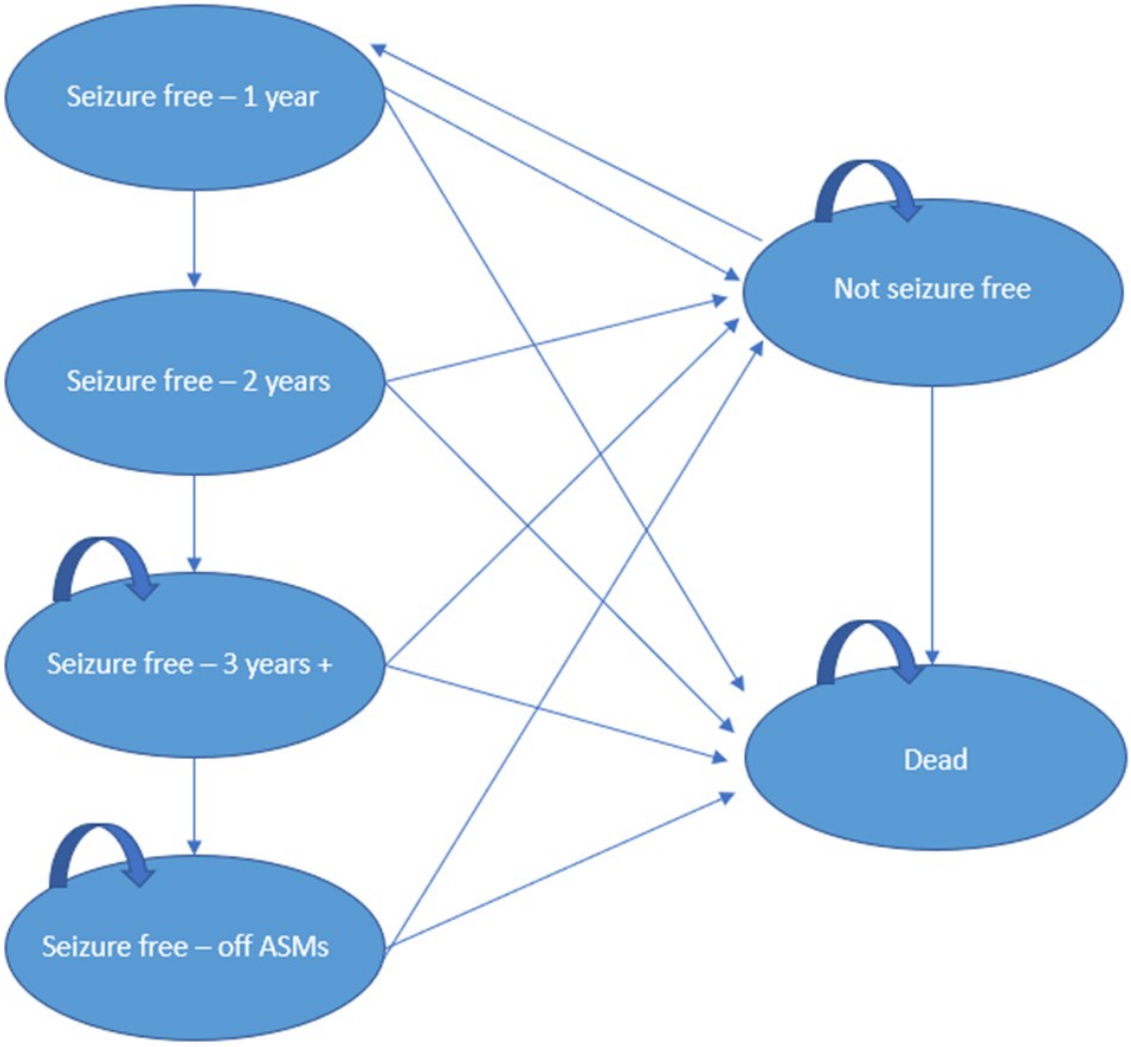
Figure 2: Model structure – Markov model



1.2.2 Uncertainty

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.

When running the probabilistic analysis, multiple runs are required to account for random variation in sampling. To ensure the number of model runs were sufficient in the probabilistic analysis we checked for convergence in the incremental costs, QALYs and net health benefit at a threshold of £20,000 per QALY gained for surgery versus medical management. This was done by plotting the number of runs against the mean outcome at that point (see example in Figure 3) for the base-case analysis. Convergence was assessed visually, and each outcome had stabilised before 2000 runs.

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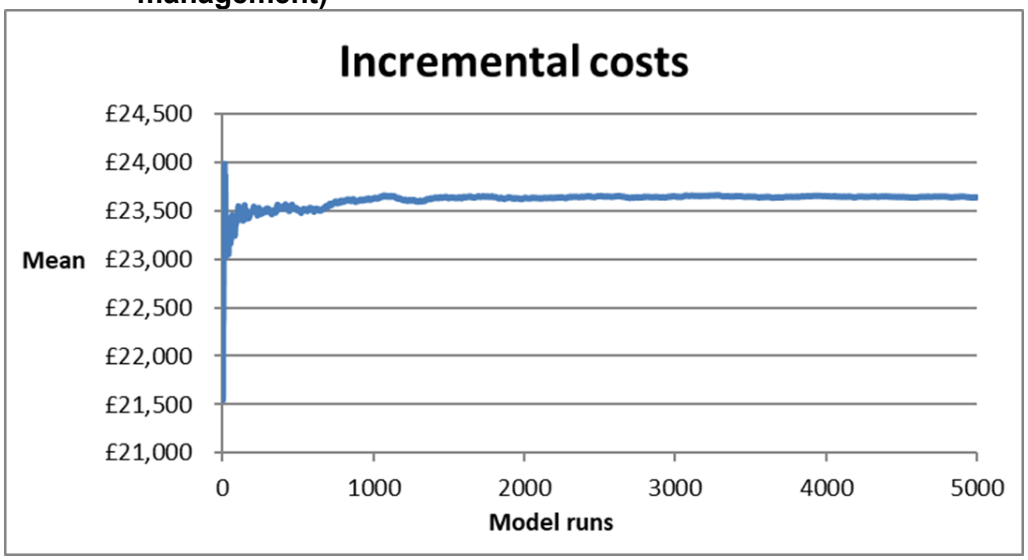
Figure 3: Checking for convergence: incremental costs (Surgery vs Medical management)



The way in which distributions are defined reflects the nature of the data, so for example event probabilities were given a beta distribution, which is bounded by 0 and 1, reflecting that the probability of an event occurring cannot be less than 0 or greater than 1. All of the variables that were probabilistic in the model and their distributional parameters are detailed in Table 1, Table 2, and in the relevant input summary tables in sections 1.3.3 and 1.3.3.5. Probability distributions in the analysis were parameterised using error estimates from data sources.

Table 1: Description of the type and properties of distributions used in the probabilistic analysis

Parameter	Type of distribution	Properties of distribution
Probabilities	Beta	Bounded between 0 and 1. As the sample size and the number of events were specified, the distribution parameters were calculated as follows: • Alpha = (number of patients hospitalised) • Beta = (number of patients) − (number of patients hospitalised)
Risk ratios Standardised mortality ratios	Lognormal	The natural log of the mean and standard error were calculated as follows: • Mean = ln(mean cost) − $SE^2/2$ • SE = [ln(upper 95% CI) − ln(lower 95% CI)]/(1.96×2) $\sqrt{\ln \frac{SE^2 + mean^2}{mean^2}}$ This formula includes a correction to ensure the mean generated in the probabilistic analysis will be the same as the reported mean. [2]
Utility decrements Resource use Surgery costs	Gamma	Bounded at 0, positively skewed. Derived from mean and its standard error. Alpha and beta values were calculated as follows: • Alpha = $(mean/SE)^2$ • Beta = SE^2/Mean

Abbreviations: 95% CI = 95% confidence interval; SE = standard error.

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The following variables were left deterministic (that is, they were not varied in the probabilistic analysis):

- the cost-effectiveness threshold
- the probability of discontinuing Anti-seizure Medication (ASM)
- probability of reoperation
- probability of long-term complications from resective epilepsy surgery
- the proportion of people obtaining a ≥50% reduction in seizures and a <50% reduction in seizures
- appointment costs
- admission costs
- ASM costs

In addition, various deterministic sensitivity analyses were undertaken to test the robustness of model assumptions. In these, one or more inputs were changed, and the analysis rerun, to evaluate the impact on results, and whether conclusions on which intervention should be recommended, would change. Details of the sensitivity analyses undertaken can be found in methods section 1.5.

1.3 Model inputs

1.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. Model inputs were validated with clinical members of the guideline committee. A summary of the model inputs used in the base-case (primary) analysis is provided in Table 2 below. More details about sources, calculations and rationales for selection can be found in the sections following this summary table.

Table 2: Overview of parameters and parameter distributions used in the model

Input	Data	Source	Probability distribution
Comparators	• Epilepsy surgery[(a)] • Medical management		n/a
Population	Adults with drug refractory epilepsy		n/a
Perspective	UK NHS & PSS	NICE reference case[23]	n/a
Time horizon	Lifetime		n/a
Discount rate	Costs: 3.5% Outcomes: 3.5%	NICE reference case[23]	n/a
Cohort settings			
Cohort starting age	35	Wiebe 2001[44]	n/a
Percentage of people entering the model that are male	46.7%	de Tisi 2011[11]	n/a
1-year decision tree			

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Input	Data	Source	Probability distribution
Probability of not being seizure free MM	96.7%	Wiebe 2001[44] & Engel 2012[13]	Beta Alpha = 59, Beta = 2
Risk ratio	0.42	Wiebe 2001[44] & Engel 2012[13]	Lognormal LnRR = -0.87, SE = 0.16
Probability of mortality in the surgery arm	0.77%	de Tisi 2011[11]	Beta Alpha = 5, Beta = 644
Probability of long-term complication from resective epilepsy surgery	4.0%	Committee opinion[(a)]	n/a
Long-term Markov model			
Probability of discontinuing ASMs each year ≥ 3 years of seizure freedom	15.7%	Burch 2012[6]	n/a
General population mortality	Age and sex dependent	ONS Life Tables[31]	n/a
Seizure free SMR surgery	2.42	Weighted average of other two SMRs - See 1.3.4	n/a
Seizure free SMR MM	1.78	Salanova 2002[36]	Lognormal LnRR = 0.575, SE = 0.678
Not seizure free SMR	5.40	Choi 2008[9]	Lognormal LnRR = 1.686, SE = 0.158
Probability of relapse surgery	Various values. Please see Table 4	de Tisi 2011 [11]	Beta
Probability of remission surgery	Various values. Please see Table 5	de Tisi 2011 [11]	Beta
Probability of remission each year MM	5.6%	Callaghan 2011[8]	5-year probability Beta[(d)] Alpha = 62, Beta = 184
Probability of relapse each year MM	22.0%	Callaghan 2011[8]	5-year probability Beta[(c)] Alpha = 42, Beta = 17
Probability of reoperation	4.0%	Committee opinion	n/a
Health-related quality of life (utilities)			
Full health	1.000	By definition	n/a
Seizure free surgery	0.858	Väätäinen 2020[43] [(b)]	See Table 8[(e)]
Seizure free MM	0.869	Väätäinen 2020[43]	See Table 8 [(e)]
Not seizure free surgery / MM	0.689	Väätäinen 2020[43(c)]	See Table 8 [(e)]
Dead	0	By definition	n/a
Costs			
Pre-surgical evaluation			
Probably of being a surgery candidate	41.3%	Epilepsy pre-surgical evaluation survey	Beta

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Input	Data	Source	Probability distribution
			Alpha = 274, Beta = 380
Pre-surgical evaluation	£8,182	See Table 9	Gamma or beta distribution for the usage of each specific assessment
Surgery			
Surgery	£10,185.16	NHS reference costs 2018/19[28]	Gamma Mean=10,185.16 SE=Mean/5
Complications			
Cost per year for complications from surgery	£5,000	Committee opinion(f)	n/a
Appointment costs			
Neurology appointment seizure free surgery years 1-2	£262.13	See Table 11	n/a
Neurology appointment seizure free MM years 1-2	£209.70	See Table 11	n/a
Neurology appointment seizure free surgery years 3+	£59.48	See Table 11	n/a
Neurology appointment seizure free MM years 3+	£268.87	See Table 11	n/a
GP costs seizure free	£13.32	See Table 11	n/a
GP costs not seizure free	£45.15	See Table 11	n/a
Admission costs			
Inpatient and A&E admissions seizure free	£27.79	See Table 12	n/a
Inpatient and A&E admissions not seizure	£435.20	See Table 12	n/a
Drug costs			
ASM drugs per day	2.5	Committee opinion	n/a
ASM cost per drug	£416.90	See Table 13	n/a

Abbreviations: A&E = Accident & Emergency, ASMs = Anti-seizure medications, MM = Medical management, SMR = Standardised mortality ratio

(a) The committee discussed the probability of long-term complications post-surgery and referred to a 2013 systematic literature review[14] where the probability of major complications from surgery was 4.7%. The committee did however note that the probability of long-term complications form resective epilepsy surgery is decreasing, making reference to a more recent 2021 publication[3].

(b) Weighted to account for a proportion of people reported in de Tisi 2011 who were not completely seizure free and still experienced simple partial seizures , now referred to as focal aware seizures (FAS). 82% of people in de Tisi 2011 were completely seizure free at end of follow-up. The SMR for seizure free was applied for these 82% of people and the SMR for not seizure free was applied to the remaining 18% of people who were not completely seizure free

(c) In Väätäinen 2020 the utility values were reported for people with a ≥50% reduction and seizures and a <50% reduction seizures so the proportion of people achieving a ≥50% reduction and seizures and a <50% reduction seizures was weighted by values reported in Neligan 2011[27]

(d) A beta distribution was applied to the cumulative probability at 5 years and the probabilistic probability at 5 years was converted to a rate and an annual probability

(e) A Gamma distribution was used because the probabilistic utility values were calculated to maintain rank. Utility decrements were calculated, and a Gamma distribution was applied to these utility decrements.

(f) The committee estimated the cost of long-term complications to be £5,000: cognitive deficits would not incur a cost to the NHS and major visual field defects would incur a small cost to the NHS. Stroke (and haemorrhage) would lead to the most significant costs to the NHS. A stoke may incur high initial costs of rehabilitation but these high costs are unlikely to be continuous for the majority of people.

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1.3.2 Initial cohort settings

The starting age for people in the model was 35. The average age of people in the model was based on the larger RCT[44] included in the clinical review, assessing the effectiveness of surgery in adults. In Wiebe 2001[44] there were 40 people in each arm of the trial (surgery versus medical therapy whilst waiting for surgery). The average age of people in the surgery arm was 35.5 and the average age of people in the medical management arm was 34.4. In Engel 2012[13] there were 15 people in the surgery arm and 23 people in the medical management arm. The average age of people in the surgery arm was 37.5 and the average age of people in the medical management arm was 30.9.

The proportion of males in the model was 46.7%. This value was obtained from de Tisi 2011[11] which informed the long-term outcomes for resective epilepsy surgery to be used in the cost effectiveness analysis.

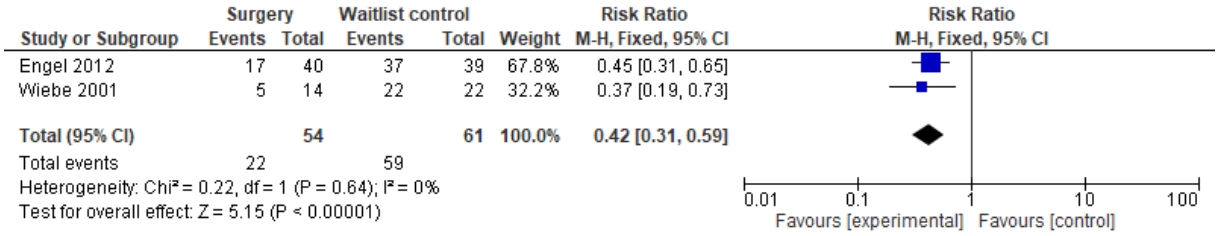
1.3.3 Short-term outcomes

A two-arm decision tree was used to model the 1-year outcomes for surgery and medical management. At the end of one-year patients could be, seizure free, not seizure free or have died.

1.3.3.1 Probability of having seizures

The probability of seizures for people receiving medical management was estimated using data included in the clinical review[13, 44].

Figure 4: Seizures at one-year - Surgery versus waiting list



The probability of seizures for medical management was calculated from the waiting list arms of the trials since these patients were being medically managed while waiting for surgery - see Figure 4. Two of these patients did not have any seizures by 12 months despite having seizures at least monthly prior to randomisation. This resulted in a probability of having seizures of 96.7% (59/61).

The probability of seizures for surgery was calculated by multiplying the probability of seizures for medical management with the pooled risk ratio of 0.42 – see Figure 4. This resulted in a probability of 40.6% for not being seizure free after epilepsy surgery.

A beta distribution was applied to the probability of being seizure free in the medical management arm and a lognormal distribution was applied to the risk ratio in the probabilistic analysis.

A one-way sensitivity analysis was conducted using data only from Wiebe 2001 of which details can be found in section 1.5.6.

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1.3.3.2 Probability of mortality for the surgery arm

Mortality for the first year after resective epilepsy surgery (including operative mortality) was estimated from de Tisi 2011[11]. Various data inputs were sourced for operative mortality[7, 12, 15, 17, 21, 32-35, 37, 42] however these studies only provided data on the risk of operative mortality and did not provide data for all-cause mortality within 1-year after surgery. Conversely, mortality reported in de Tisi 2011[11] included operative mortality as well as mortality from other causes. Therefore, because de Tisi[11] was used to inform the long-term outcomes of epilepsy surgery in our health economic analysis this was deemed the most appropriate value to use.

In de Tisi 2011[11] 5 people of the of 649 people in the total cohort died within 1 year of surgery. This resulted in a probability of 0.77% for mortality within one year after resective epilepsy surgery.

A beta distribution was applied to this probability in the probabilistic analysis.

1.3.3.3 Probability of mortality for medical management arm

Mortality for the first year in the medical management arm was a weighted average based on the proportion of people who had seizures or were seizure free. See section 1.3.4.

The probability of mortality in the medical management arm was calculated using the following formula:

$$p_{mortality\ MM} = (p_{NSF\ MM} * p_{mortaltiy\ NSF\ MM}) + p_{mortality\ SF\ MM} * (1 - p_{NSF\ MM})$$

Where p is probability, NSF is not seizure free, SF is seizure free, and MM is medical management.

This resulted in the probability of mortality at year 1 in the medical management arm of 0.39%.

A beta distribution was applied to this probability for the probabilistic analysis.

1.3.3.4 Probability of a long-term complication from resective epilepsy surgery

The clinical evidence showed that surgery was associated with several complications, including infections, bleeding and change of mood. However, most of these adverse events do not have long-term consequences for the person or the NHS.

The probability of experiencing a long-term complication from resective epilepsy surgery was assumed to be 4.0%. This was based on expert and committee opinion.

The committee noted some of the potential long-term complications a person may experience as a result of resective epilepsy surgery:

- Stroke (including haemorrhage)
- Visual field defect
- Cognitive defect

The committee discussed that the probability of long-term complications after resective epilepsy surgery are rare, and in recent years have become increasingly rarer. The committee made reference to a systematic literature review published in 2013[14] which noted 4.7% of patients had a major neurological complication after resective epilepsy surgery, with the most common major long-term complication being a visual field defect (2.1%). The committee also noted a more recent publication from 2021[3] which illustrates long-term complications from resective epilepsy surgery are now rarer. Therefore, the committee concluded the probability of a long-term complication of 4.0% would be an appropriate value to use and might be an overestimate.

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1.3.3.5 Longer-term outcomes

Transition probabilities were calculated for the risk of relapse and remission for both medical management and surgery. This risk of relapse is defined as the probability of transitioning from seizure free to not seizure free and the risk of remission is defined as the probability of transitioning from not seizure free to seizure free. The probability of relapse and remission for people undergoing epilepsy surgery was estimated based on values reported in de Tisi 2011[11] and the probability of relapse and remission for medical management was estimated based on values reported in Callaghan 2011[8].

1.3.3.6 Probability of relapse and remission for surgery

de Tisi 2011 [11] is UK prospective cohort study of 615 adults undergoing resective epilepsy surgery. The number of people relapsing and entering remission after surgery was presented in a graph (Figure 3) which provided a breakdown of the number of people in four distinct categories. These categories are presented in Table 3.

Table 3: Categorisation of states in de Tisi 2011

	Category
Category 1	Seizure free this year and not seizure free the subsequent year
Category 2	Seizure free this year and seizure free the subsequent year
Category 3	Not seizure free this year and seizure free next year
Category 4	Not seizure free this year and not seizure free the subsequent year

Data for the number of people in each category was provided up to and including year 15, however the number of people lost to follow-up increased yearly. Data were extracted from the graph using DigitizeIt to determine the total number of people residing in each category presented in Table 3.

The probability of relapse was calculated by dividing the number of people who were seizure free this year and not seizure free the subsequent year (Category 1) by the total number of people who were seizure free this year. The number of people residing in each state (Category 1 and Category 2) and the corresponding probabilities for each year up to year 15 are presented in Table 4.

Table 4: The probability of relapse for surgery up to year 15

Cycle	Year	Seizure free this year and not seizure free the subsequent year	Seizure free this year and seizure free the subsequent year	Probability
1	2	390	351	10.0%
2	3	363	332	8.5%
3	4	329	306	7.0%
4	5	295	279	5.4%
5	6	272	260	4.4%
6	7	247	237	4.0%
7	8	223	218	2.2%
8	9	208	197	5.3%
9	10	180	169	6.1%
10	11	150	144	4.0%
11	12	128	124	3.1%
12	13	104	102	1.9%
13	14	82	79	3.8%

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Cycle	Year	Seizure free this year and not seizure free the subsequent year	Seizure free this year and seizure free the subsequent year	Probability
14	15	51	46	8.3%

Because data were only available to populate the Markov model up to year 15 (cycle 14 of the Markov model) the data for the remaining lifetime horizon of the model needed to be extrapolated. Beyond year 5 there was no clear trend in the data, so a constant hazard was estimated using the data from year 6 to year 15. This resulted in an annual probability of relapse of 4.2% (68/1,644), which was applied in the model from year 16 onwards.

The probability of remission was calculated by dividing the number of people who were not seizure free this year and seizure free next year (Category 3) by the total number of people who were not seizure free this year. The resulting probabilities for remission up to year 15 are presented in Table 5.

Table 5: The probability of remission for surgery up to year 15

Cycle	Year	Not seizure free this year and seizure free next year	Not seizure free this year and not seizure free the subsequent year	Probability
1	2	168	123	26.8%
2	3	142	121	14.8%
3	4	137	115	16.1%
4	5	131	110	16.0%
5	6	122	107	12.3%
6	7	111	99	10.7%
7	8	102	92	10.1%
8	9	86	75	12.3%
9	10	71	67	6.0%
10	11	68	65	5.4%
11	12	54	48	11.3%
12	13	43	40	7.0%
13	14	30	28	8.0%
14	15	21	20	6.2%

Once again, because data were only available to populate the Markov model up to year 15 (cycle 14) the data for the remaining lifetime horizon of the model needed to be extrapolated. Beyond year 10 there was no clear trend in the data, so a constant hazard was estimated using the data from year 11 to year 15. This resulted in an annual probability of relapse of 7.6% (16/216), which was applied in the model from year 16 onwards.

The committee acknowledged that the probability of remission form year 16 onwards was calculated based on a significantly smaller sample size compared to the data used for relapse (216 compared to 1,644). However, calculating the probability of remission using data from year 6 to year 15, as was done for the probability of relapse, resulted in a probability of remission of 9.7%. The committee concluded that a probability of 9.7% for remission from year 16 onwards would very likely be overestimating the probability of remission.

A beta distribution was applied to both these probabilities for the probabilistic analysis.

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1.3.3.7 Probability of relapse and remission for medical management

The probability of relapse and remission for medical management was based on values reported in Callaghan 2011[8]. They reported values of remission and relapse for up to 5 years for a cohort of 246 patients followed prospectively at a single epilepsy centre in the USA.

The risk of relapse and remission was reported as a cumulative probability at 5 years. Therefore, the cumulative probability at 5 years needed to be converted to an annual probability to be used in the health economic model. Assuming the rate of relapse and remission was constant over the 5-year period, the five-year probability was converted into a rate:

$$r = \frac{-ln(1-p)}{t}$$

Where p is the probability, r is the yearly hazard rate, ln is the natural log and t is the time, in this case 5 years.

It is then converted in to a 1-year probability, as follows:

$$p = 1 - exp(-rt)$$

Where p is the probability, r is the yearly hazard rate and t this time is 1 year.

The five-year probability of relapse was reported as 71.20% and the five-year probability of remission was 25.2%. Using the formula outlined above this resulted in an annual probability of relapse of 22.0% and an annual probability of remission of 5.6%.

A beta distribution was applied to both the pre-conversion probabilities for the probabilistic analysis.

1.3.3.8 Discontinuation of Anti-Seizure Medications

If people had been seizure free for three or more years, then they had an annual probability of 15.7% for discontinuing their Anti-Seizure Medication (ASM). This probability was obtained from Wieser 2003[45].

1.3.3.9 Probability of reoperation

For people who receive resective epilepsy surgery a 4% probability of reoperation was assumed. This is because for a small proportion of people initial resective epilepsy surgery will be unsuccessful because, for example, the entire epileptic zone was not fully resected. Subsequently, this group of people will undergo a series of tests in line with those received for assessment for resective epilepsy surgery to identify the remainder of epileptic zone which has the potential to be resected. This probability of 4.0% was based on committee opinion. For simplicity, operations were assumed to take place at 5 years (cycle 4 in the Markov model).

1.3.4 Life expectancy

Overall life expectancy was incorporated in the model in the following way:

- Risk of death associated with epilepsy surgery
- Standardised mortality ratios (SMRs) for seizure free (surgery and medical management) and not seizure free were applied to the general population mortality rates from Office of National Statistic (ONS) life tables[31]

Mortality in the first year after surgery was estimated based on values reported in de Tisi 2011[11] as outlined in section 1.3.3.2. The risk of surgical mortality was also incorporated into

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the model for those people who have a reoperation. This probability was calculated by taking the difference between mortality in the surgery arm and mortality in the medical management arm for 1-year and resulted in a probability of surgical mortality of 0.38%.

SMRs for seizure free surgery, seizure free medical management, and not seizure free were also applied to the general population mortality rates to estimate the probability of a person dying from epilepsy related causes or all-cause mortality throughout the lifetime horizon of the model. The death rate for seizure free surgery, seizure free medical management, and not seizure free was calculated using the following formulae:

$$Death\ Rate_{SF\ Surgery} = Death\ Rate_{general\ population} * SMR_{SF\ surgery}$$

$$Death\ Rate_{SF\ Medical\ Management} = Death\ Rate_{general\ population} * SMR_{SF\ medical\ management}$$

$$Death\ Rate_{NSF} = Death\ Rate_{general\ population} * SMR_{NSF}$$

These rates were then converted to probabilities to be inputted into the Markov model using the following formula:

$$p = 1 - exp(-r)$$

Where p is the probability and r is the rate.

The SMR for seizure free was obtained from Salanova 2002[36]. This study was one of the two studies used to obtain the pooled SMR for seizure free in Choi 2008[9]. Choi 2008[9] was the study used to model the long-term outcomes in the Health Technology Assessment (HTA) which was included in the epilepsy surgery evidence review. The pooled SMR from Choi 2008[9] was also used in Kovacs 2021[18] which was the other included health economic study in the epilepsy surgery review.

Salanova 2002[36] estimated the SMR for people who are seizure free to be 1.78. Sperling 1999[41] was the additional study used to obtain the pooled SMR in Choi 2008 which estimated the number of deaths to be 0. Therefore, the overall pooled SMR reported in Choi 2008[9] was 1.11. The committee noted that the inclusion of a study that had no deaths might lead to the SMR being under-estimated. Therefore, they concluded that it would be more appropriate to use the SMR of 1.78 reported in Salanova 2002[36] in the base case analysis and use the pooled SMR reported in Choi 2008[9] in a sensitivity analysis. Details of this sensitivity analysis can be found in 1.5.7.

de Tisi 2011[11] was the long-term outcome study used to inform the long-term outcomes after epilepsy surgery. However, seizure freedom in de Tisi 2011[11] was defined as either completely seizure free or seizure free except for simple partial seizures (now termed focal aware seizures, FAS). Conversely, Callaghan 2011[8], which was used to inform the long-term outcomes of medical management, defined seizure freedom as completely seizure free. Therefore, an adjustment to the SMR for people who were seizure free in the surgery arm was applied to account for the number of people who were seizure free in the surgery arm who were not completely seizure free (i.e., a proportion of people still experienced focal aware seizures). It was calculated from de Tisi 2011[11] that 82% of people at the end of follow-up were completely seizure free. Therefore, the SMR for people seizure free surgery in the surgery arm in the following way:

$$SMR_{seizure\ free\ surgery} = \left(SMR_{seizure\ free} * 0.82\right) + \left(SMR_{not\ seizure\ free} * (1 - 0.82)\right)$$

SMRs for not seizure free for surgery and medical management were also reported in Choi 2008[9]. The SMR reported in Choi 2008[9] for not seizure free surgery was 5.64 and the SMR for not seizure free medical management was 5.40. The SMR for not seizure free surgery was calculated by pooling two SMRs together[36, 41] and the SMR for not seizure free surgery

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was calculated by pooling three SMRs[1, 22, 30] together. The committee noted that the SMRs for both surgery and medical management were effectively the same.

The resulting SMRs applied to the general population mortality rates are presented in Table 6.

Table 6: Standardised mortality ratios

	SMR
Seizure free surgery	2.42
Seizure free medical management	1.78
Not seizure free	5.40

A lognormal distribution was applied to the SMRs for the probabilistic analysis.

1.3.5 Utilities

Utilities for people who are seizure free and not seizure free were based on values from Väätäinen 2020[43]. The values cited in Väätäinen 2020[43] were based on EQ-5D data from the SANAD study. These utility values were also used in the health economic model assessing the cost effectiveness of different ASMs developed for this guideline. The utility values reported in Väätäinen 2020 are reported in Table 7.

Table 7: Utility values reported in Väätäinen 2020

Health state	Utility value	Source
Full health	1.000	
Seizure free - MM	0.869	Väätäinen 2020
≥50% reduction in seizures	0.805	Väätäinen 2020
<50% reduction in seizures	0.623	Väätäinen 2020
Not seizure free	0.689	=0.805x36%+0.623*64%
Seizure free - surgery	0.858	=0.869x82%+0.805*18%

By definition the utility of full health is 1.00 and the standard error of full health is 0.00.

Because the utility values reported in Väätäinen 2020[43] provide utility values for people experiencing a ≥50% reduction in seizures and <50% reduction in seizures, data were required to calculate the utility for the not seizure free health state in our health economic model. Neligan 2011[27] reported the number of people in a drug refractory cohort of 139 people receiving medical management in the UK who achieved seizure freedom, a 50% - 99% improvement in seizures and <50% improvement in seizures. At the end of follow-up, 41 people experienced a ≥50% reduction in seizures and 72 people experienced a <50% reduction in seizures. Therefore, of the 139 people in the cohort study, 29.50% of people experienced a ≥50% reduction in seizures and 51.80% of people experienced a <50% reduction in seizures.

Therefore, of the people that were not seizure free 29.50%/[29.50%+51.80%] = 36.28% experienced a ≥50% reduction in seizures. These proportions were applied to the utility for a ≥50% reduction in seizures and the utility for a <50% reduction in seizures to obtain the utility for not seizure free – see Table 7.

The procedure outlined in section 1.3.4 used to make an adjustment for the SMR for seizure free surgery was also applied to calculate the utility of seizure free surgery to account for seizure free in de Tisi 2011 being defined as completely seizure free or only simple partial seizures , now referred to as focal aware seizures (FAS). Once again, this adjustment was

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made using data from de Tisi 2011 where 82% of people at the end of follow-up were completely seizure free. The resulting formula to calculate the utility of seizure free surgery is outlined below:

$$Utility_{seizure\ free\ surgery} = \left(utility_{seizure\ free} * 0.82\right) + \left(utility_{not\ seizure\ free} * (1 - 0.82)\right)$$

In the probabilistic analysis, the probability of being completely seizure free was also made probabilistic using a Beta distribution.

The utility value for seizure free medical management is the utility value for seizure freedom reported in Table 7.

The utility of seizure freedom in the surgery arm was calculated by combining the utility value for seizure free and the utility value for not seizure free reported in Table 7, using the formula outlined above. The utility values used in the health economic analysis for not seizure free for medical management and surgery are the values calculated by weighting the proportion of people achieving a ≥50% reduction in seizures and a <50% reduction in seizures reported by the utility values reported in Väätäinen 2020[43] (see Table 7).

To make these utility values, probabilistic utility decrements between states were calculated using the data from Väätäinen 2020[43].

The utility decrements are reported in Table 8.

Table 8: Utility decrements for the utility values reported in Väätäinen 2020

	Utility decrement	SE (20% of mean)
Decrement 1. Full health – seizure free	0.131	0.174
Decrement 2. Seizure free – ≥50% reduction in seizures	0.064	0.237
Decrement 3 ≥50% reduction in seizures – <50% reduction in seizures	0.182	0.204

The standard error of the mean utility decrements was assumed to be 20% of the mean decrement - Table 7.

Probabilistic values were then calculated for the utility decrements using a Gamma distribution. The resulting probabilistic values for the utility values reported in Väätäinen 2020[43] were calculated in the following way:

- The probabilistic utility value for seizure free was calculated by subtracting probabilistic Decrement 1 from the utility value for full health (i.e., 1).
- The probabilistic utility values for a ≥50% reduction in seizures was calculated by subtracting the probabilistic Decrement 2 from the probabilistic utility value for seizure free.
- The probabilistic utility value for a <50% reduction in seizures was calculated by subtracting the probabilistic Decrement 3 from the probabilistic utility value for a ≥50% reduction in seizures.

Using the method outlined above to obtain the probabilistic utility values keeps the utility rank the same.

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A utility decrement of 0.2 for long term complications associated with resective epilepsy surgery was also applied to the model. This utility decrement was obtained from Choi 2008[9].

1.3.6 Assessment for resective epilepsy surgery survey

Before a person can undergo resective epilepsy surgery a person must undergo a number of tests to assess if surgery is suitable for them.

A 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, all of which were used in the economic analysis.. Out of the ten surgical centres who submitted data, data was available for a total of 762patients.

Overall, fourteen epilepsy surgical centres were contacted resulting in a response rate of 71%. The committee were provided 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 average number of tests for all participating centres was calculated by summing the total number of people receiving a given test across all participating centres and dividing this by the total cohort of people. The unit cost for each respective test was then multiplied by the average number of tests to obtain the average cost of each test for a person undergoing assessment for resective epilepsy surgery.

Table 9: 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
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**

All sources for unit costs were taken from NHS reference costs 2019/20 [29] if available. The exceptions were:

(a) The committee concluded the same cost for MRI as reported in NHS reference costs could be used for fMRI

(b) A committee member provided the cost from their centre

(c) The committee estimated the cost to be between £2,000 and £5,500 so the average of these estimates was used

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(d) *The committee estimated the cost to be between £3,000 and £5,000 so the average of these estimates was used*

These costs were made probabilistic by applying either a Gamma or a Beta distribution. A Beta distribution was applied to all tests where the mean number of tests was above 1 (History & Examination, Neuropsychiatry assessment, and Multidisciplinary team meeting). A Gamma distribution was applied to the remaining preoperative assessment tests.

1.3.6.1 Probability of receiving epilepsy surgery

The centres were also asked about the outcome of patients being assessed for surgery to assess what proportion go on to have it. The probability of being a surgery candidate was estimated to be 41.3%.The numerator of this probability only included those people who were eligible for resective epilepsy surgery and surgery went ahead or was due to take place. In other words, the numerator did not include those people who were eligible for surgery but did not consent to surgery . In the model we add the test of costing those patients that didn't go on to have surgery as well as the cost of the surgical patient themselves. So, the total assessment cost per patient undergoing surgery is £8,182 + £11,628 = £19,809, where £11,628=£8,182*(58.7%)/41.3%.

A beta distribution was applied to the probability of going on to surgery for the probabilistic analysis.

Additional one-way sensitivity analyses were conducted assuming a higher proportion of people were eligible for surgery after assessment for resective epilepsy surgery and lower proportion of people were eligible for surgery after assessment for resective epilepsy surgery. Details of these sensitivity analyses can be found in sections 1.5.4 and 1.5.5 respectively.

1.3.7 Other resource use and costs

1.3.7.1 Surgery

The cost of surgery was calculated taking the weighted average of the total costs divided by the total number of Finished Consultant Episodes (FCE's). The total number of FCE's was 9,087 and the sum of the national average was £95,552,533. The total cost of surgery used in the health economic model was £10,185 (£95,552,533/9,087). The costs used in the calculation for the total cost of surgery are presented in Table 10.

Table 10: Cost of surgery

Currency Code	Currency Description	Number of FCE's	National Average Unit Cost
AA50A	Very Complex Intracranial Procedures, 19 years and over, with CC Score 12+	193	£21,725
AA50B	Very Complex Intracranial Procedures, 19 years and over, with CC Score 6-11	226	£14,974
AA50C	Very Complex Intracranial Procedures, 19 years and over, with CC Score 0-5	257	£13,003
AA51A	Complex Intracranial Procedures, 19 years and over, with CC Score 12+	317	£17,108
AA51B	Complex Intracranial Procedures, 19 years and over, with CC Score 8-11	402	£11,785
AA51C	Complex Intracranial Procedures, 19 years and over, with CC Score 4-7	686	£10,035
AA51D	Complex Intracranial Procedures, 19 years and over, with CC Score 0-3	621	£9,698

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Currency Code	Currency Description	Number of FCE's	National Average Unit Cost
AA52A	Very Major Intracranial Procedures, 19 years and over, with CC Score 12+	419	£13,477
AA52B	Very Major Intracranial Procedures, 19 years and over, with CC Score 8-11	597	£10,322
AA52C	Very Major Intracranial Procedures, 19 years and over, with CC Score 4-7	1128	£9,397
AA52D	Very Major Intracranial Procedures, 19 years and over, with CC Score 0-3	930	£9,061
AA53A	Major Intracranial Procedures, 19 years and over, with CC Score 12+	303	£12,444
AA53B	Major Intracranial Procedures, 19 years and over, with CC Score 8-11	588	£8,689
AA53C	Major Intracranial Procedures, 19 years and over, with CC Score 4-7	1245	£7,929
AA53D	Major Intracranial Procedures, 19 years and over, with CC Score 0-3	1175	£7,642
All		9087	**£10,185**

Source: NHS reference costs 2019/20 [29]

1.3.7.2 Surgery complications

Most complications are relatively minor, short-term and would be captured within the cost of the initial hospital stay. Some complications affecting cognition might last longer but would not result in additional costs for the NHS.

The committee noted there is a 1% risk of stroke after resective epilepsy surgery. The costs associated with stroke will be high if the stroke results in a permanent disability meaning the patient requires equipment, carers, and physiotherapy. However, only a small proportion of people will experience a stroke which results in a permanent disability. In the UK approximately 450 people undergo resective epilepsy surgery each year therefore approximately 4.5 people are at risk of experiencing a stroke from resective epilepsy surgery. Of these 4.5 people who experience a stroke each year the severity of the stroke will vary and approximately 1 to 2 people may be at risk of experiencing a permanent disability. The committee also noted there is a small risk of suffering a visual field defect after resective epilepsy surgery. The long-term cost of a visual field defect would be relatively small as treatment includes restorative training, optical aids, and compensatory training.

The long-term cost of complications from surgery was assumed to be £5,000 per year over the lifetime. This cost was based on committee opinion. The committee noted it was challenging to estimate the cost of long-term complications but noted an annual cost of £5,000 applied across a lifetime horizon would likely be an overestimate.

1.3.7.3 Appointments

People with epilepsy access health care services more than people without epilepsy. How frequently people access services is linked to whether a person is experiencing seizures or not. Therefore, one element of cost differences between epilepsy surgery and medical management will be dependent on the number of people rendered seizure free from the respective treatment a person receives.

Appointment costs in the model were categorised into four different costs. The cost of being seizure free 1 – 2 years after surgery, the cost of being seizure free in the first 1 – 2 years for medical management, the cost being seizure free for 3 or more years and the cost of not

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being seizure free. Appointment costs included appointments with a neurologist and appointments with a GP.

Data on the probability of service use was taken from Jacoby 1998[16] or based on committee opinion. Resource use from Jacoby and 1998[16] was multiplied by an expected number of contacts estimated by the committee. Jacoby and colleagues collected data for three groups of patients, those experiencing no seizures, less than one seizure a month, and more than one seizure a month. Our health economic analysis only has two health states where costs and utilities are applied (seizure free and not seizure free) and the not seizure free health state does not differentiate between people experiencing less than one seizure a month and more than one seizure a month. Overall, the difference between service use for people experiencing less than one seizure a month and more than one seizure a month reported in Jacoby 1998[16] was relatively small. Therefore, the service use associated with experiencing more than one seizure per month is used in the model for all people who are not seizure free. Unit costs and resource use summarised in Table 11.

Table 11: Cost of outpatient contacts

Category	State	Mean resource use per year	Unit cost	Mean cost per year
Neurology – First appointment (consultant-led non-face-to-face)(a)	Seizure free year 1-2	0(c)	£120.76	£0
	Seizure free year 3+	18%(d)		£21.74
	Not seizure free	49%(d)		£59.17
Neurology - follow-up (consultant-led non-face-to-face)(a)	Seizure free year 1-2 surgery	2.5(c)	£104.85	£262.13
	Seizure free year 1-2 MM	2(c)		£209.70
	Seizure free year 3+	18%(d) x 2 visits(c)		£37.75
	Not seizure free	100%(c) x 2 visits(c)		£209.70
GP consultation(b)	Seizure free	18%(d)	£37.00	£13.32
	Not seizure free	61%(d)		£45.14

Sources:

(a) NHS reference costs 2019/20 [29]
(b) PSSRU 2020, GP consultation (9.22 minutes), including qualification costs and direct care costs [10]
(c) Committee opinion
(d) Jacoby 1998[16]

1.3.7.4 Admissions

As outlined in section 1.3.7.3, data on the probability of service use was taken from Jacoby 1998[16] and multiplied by an expected number of contacts estimated by the committee. The costs for admissions are presented in Table 12.

Table 12: Cost of admissions for seizure free and not seizure free patients

	Probability of use				Cost (£)	
	Seizure free (a)	Not seizure free (b)	Expected number of visits given non-zero use (c)	Unit cost (d)	Seizure free (=a*c*d)	Not seizure free (=b*c*d)
Inpatient	0.01	0.16	1	£2,403	£24.03	£384.44
A&E	0.02	0.27	1	£188	£3.76	£50.76
Expected total cost per patient					**£27.79**	**£435.20**

Sources:

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(a) Annual probability of accessing a service if seizure free, from Jacoby 1998[16]
(b) Annual probability of accessing a seizure if experiencing one seizure per month, from Jacoby 1998[16]
(c) Committee opinion and previous guideline [24]
(d) NHS references costs 2019/20[29]

1.3.7.5 Drugs

It was assumed patients in the model would receive on average 2.5 ASMs a day. Some people could discontinue ASMs if they have been seizure free for 3 or more years – see 1.3.3.8.

The committee provided information on what ASMs people would receive with drug refractory epilepsy and estimated the proportions of people who would be receiving each drug. The committee noted that people with drug refractory epilepsy would most likely be receiving Carbamazepine, Levetiracetam, or Lamotrigine therefore a 20% weighting was applied to these three ASMs. The committee also noted it was possible, but unlikely, people would receive Pregabalin or Gabapentin and therefore concluded a 0.3% weighting for these drugs should be applied to the total cost for these ASMs. For simplicity an equal weighting was applied to the remaining ASMs. The source of dosages for each drug were based on committee opinion and the British National Formulary (BNF). Dosages were assumed to be the average or upper range because people with drug refractory epilepsy are more likely to be on higher dosages of ASMs. Information on the drugs included in the costing of ASMs is presented in Table 13.

Table 13: 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)[4]
(c) BNF[4], Date accessed: 16/05/21

The total average cost for one ASM was calculated to be £417. This figure was multiplied by 2.5 to obtain the total yearly costs for ASMs per person (£1,042).

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1.4 Computations

The model was constructed in Microsoft Excel 2010 and was evaluated by decision tree and cohort simulation. Time dependency was built in by cross referencing tables containing relapse rate, remission rate and death rate by cycle Mortality was determined by age. Relapse and remission were determined by time since surgery.

Life years for the cohort were computed each cycle. To calculate QALYs for each cycle, the proportion of the cohort in each state was multiplied by a utility score for that state. A half-cycle correction was applied.

QALYs were then discounted to reflect time preference (discount rate 3.5%). The total discounted QALYs were the sum of the discounted QALYs per cycle.

Costs per cycle, C(t), were calculated in the same way as QALYs. Costs were discounted to reflect time preference (discount rate 3.5%) in the same way as QALYs using the following formula:

Discounting formula:

$\text{Discounted total} = \frac{\text{Total}}{(1+r)^n}$	Where: *r*=discount rate per annum *n*=time (years)

In the deterministic and probabilistic analyses, the total number of QALYs and resource costs accrued for each arm was recorded. I. The total cost and QALYs accrued by the cohort was divided by the number of patients in the population to calculate a cost per patient and QALYs per patient.

1.5 Sensitivity analyses

In addition to the probabilistic analysis, a range of one-way sensitivity analyses were undertaken:

1. Utilities assuming 50% of people in the surgery arm have a ≥50% reduction in seizures
2. Utilities from Kovacs 2021
3. Utilities from the previous NICE guideline
4. The probability of receiving surgery is higher
5. The probability of receiving surgery is lower
6. Treatment effects from Wiebe 2001 only
7. SMR for seizure free is 1.11
8. Surgery relapse rate higher
9. Surgery relapse rate lower
10. Pre-surgical evaluation costs higher
11. Pre-surgical evaluation costs lower
12. Surgery cost higher
13. Surgery cost lower
14. Time horizon 15 years
15. No discontinuation of ASMs
16. Overall best case
17. Overall worst case

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1.5.1 Utilities assuming 50% of people in the surgery arm have a ≥50% reduction in seizures

In 1.3.5 it was noted that the utility values for not seizure free had to be calculated weighting the proportion of people who achieved a ≥50% reduction in seizures and a <50% reduction in seizures reported in Neligan 2011[27] by the utility values reported in Väätäinen 2020[43]. Because Neligan 2011[27] provided data on the proportion of people who achieved a ≥50% reduction in seizures and a <50% reduction in seizures for a drug refractory cohort receiving medical management a sensitivity analysis was conducted based on the assumption that people who receive surgery would receive a greater level of reduction in their seizures. This altered the utility value for not seizure free surgery from the base case value 0.689 to 0.714. The utility values used in the health economic model when 50% of people have a ≥50% reduction in seizures (compared to 36.28% in the base case) are presented in Table 14.

Table 14: Utility values used in the health economic model when 50% of people in the surgery arm have a ≥50% reduction in seizures

Health state	Utility value
Seizure free medical management	0.869
Seizure free surgery	0.858
Not seizure free medical management	0.689
Not seizure free surgery	0.714

1.5.2 Utilities for Kovacs 2021

Using the method outlined in 1.3.5 utility values from Kovacs 2021[18] were used in a one-way sensitivity analysis - Table 15.

Table 15: Utility values used in the health economic model using utility values from Kovacs 2021

Health state	Utility value
Seizure free medical management	0.894
Seizure free surgery	0.831
Not seizure free medical management	0.543
Not seizure free surgery	0.543

1.5.3 Utilities from the previous NICE guideline

The utility values reported in the study used to calculate the utility values in the base case (Väätäinen 2020) were 0.869, 0.805, and 0.623 for seizure free, a ≥50% reduction in seizures, and <50% reduction in seizures respectively.

The utility values used in the previous NICE guideline model [24] assessing the cost effectiveness of different ASMs for monotherapy and add-on therapy had a smaller utility difference compared to those reported in Väätäinen 2020[43]. The utility difference between seizure free and a <50% reduction in seizures in the previous NICE guideline model was 0.1 compared to 0.246 from the values reported in Väätäinen 2020[43].

It is not clear why the utility values from the previous NICE guideline model are quite different but the ones from Väätäinen 2020[43] were preferred in the base case because they were from a larger sample size (n=716 vs n=125) in a slightly more recent population. The ones in the previous model also seemed implausibly high, being above the general population mean on average.

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The utilities from the previous NICE guideline model were used in a one-way sensitivity analysis. The same methods outlined in 1.3.5 were used to calculate the utility values used in the health economic model. The utility values used in the model for the sensitivity analysis are presented in Table 16.

Table 16: Utility values from the previous NICE guideline

Health state	Base case	Previous guideline model
Seizure free medical management	0.869	0.940
Seizure free surgery	0.858	0.933
≥50% reduction in seizures	0.805	0.900
<50% reduction in seizures	0.623	0.840
Not seizure free	0.689	0.862

The overall utility difference for seizure free medical management and not seizure free (medical management & surgery) is lower using the utility values from the previous NICE guideline. The utility difference using values from the previous NICE guideline is 0.078 compared to 0.18 in the base case analysis.

1.5.4 The probability of receiving surgery is higher

Out of the nine epilepsy surgery centres who submitted data as part of the assessment for resective epilepsy surgery survey, two centres calculated probability of being a surgery candidate was 60%. This value of 60% was the highest probability out of all the participating centres and therefore used in the sensitivity analysis.

1.5.5 The probability of receiving surgery is lower

The lowest probability of being a resective epilepsy surgery candidate of the individual nine participating centres was 26%.

1.5.6 Treatment effects from Wiebe 2001 only

In the base case analysis the probability of not being seizure free in the surgery arm was estimated using both studies included in the clinical review[13, 44]. However, a sensitivity analysis was conducted using the treatment effects from Wiebe 2001. This is because Engel 2012 was a smaller RCT compared to Wiebe 2001 due to the trial terminating early due to poor recruitment.

The probability of not being seizure free using data from Wiebe 2001 was calculated as the total number of events of events divided by the total number of people (37/29) resulting in a probability of 94.9%.

The probability of not being seizure free for surgery was calculated by multiplying the risk ratio (0.45) by the probability of not being seizure free for medical management (94.9%). This resulted in a probably of 42.71% for not being seizure free after epilepsy surgery compared to 40.6% in the base case.

1.5.7 SMR for seizure free is lower

As outlined in section 1.3.4 the pooled SMR reported in Choi 2008[9] was 1.11. This was used in the sensitivity analysis. However, the committee concluded it would be more appropriate to use the SMR of 1.78 reported in Salanova 2002[36] in the base case because the other study[41] which was used to obtain the pooled SMR reported in Choi 2008[9] reported zero deaths.

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1.5.8 Surgery relapse rate higher

A scenario analysis was conducted assuming the relapse rate in the surgery arm was 20% higher.

1.5.9 Surgery relapse rate lower

A scenario analysis was conducted assuming the relapse rate in the surgery was 20% lower.

1.5.10 Assessment for resective epilepsy costs higher

The highest total assessment cost across the 9 centres was £13,178.

1.5.11 Assessment for resective epilepsy costs lower

The lowest total assessment cost across the 9 centres was £5,474.

1.5.12 Surgery costs higher

A sensitivity analysis was conducted assuming a higher total cost for epilepsy surgery.

This cost was calculated by estimating the total average weighted cost for complex intracranial procedures (AA50A – AA50C), which was £16,152.

1.5.13 Surgery costs lower

A sensitivity analysis was conducted assuming a higher total cost for epilepsy surgery.

This cost was calculated by estimating the weighted average cost for major intracranial procedures (AA53A – AA53D), which was £8,376.

1.5.14 Time horizon 15 years

RCT data was only available for up to 2 years. In addition, the data to inform the long-term outcomes was only available for up to 15 years in the surgery arm and 5 years in the medical management arm therefore a sensitivity analysis was conducted using a time horizon of 15 years.

1.5.15 No discontinuation of anti-seizure medication

Discontinuation of ASMs was assumed to 15.7%[45] for people who were seizure free for 3 or more years. However, a sensitivity analysis was conducted assuming no discontinuation of ASMs because of the uncertainty surrounding the number of people who choose to come of ASMs.

1.5.16 Higher cost for Stereoelectroencephalography (sEEG)

The cost of sEEG was included as part of the total cost for preoperative assessment for resective epilepsy surgery. The committee highlighted the NHS reference cost for sEEG used in the base case analysis was likely more reflective of the cost for simple cases of sEEG. Therefore, a sensitivity analysis was conducted assuming a higher total cost for sEEG.

In this sensitivity analysis we assumed 60% of people undergoing sEEG received a simple sEEG and 40% of people received a more complex sEEG. For the simple cost of sEEG we used the NHS reference cost (£14,638) and for the more complex sEEG's we averaged the

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cost for complex cases provided by two participating surgical centres from the preoperative evaluation survey (£39,577). This resulted in a total cost for sEEG of £24,613.

1.5.17 Overall best case

The overall best-case scenario analysis combined all the assumptions most favourable to resective epilepsy surgery. These assumptions were:

- the lower cost for surgery (£8,376)
- the lower average cost for assessment for resective epilepsy surgery (£5,474)
- 20% lower relapse rate for resective epilepsy surgery
- the standardised mortality ratio for seizure free was 1.11
- a higher proportion of people were eligible surgery candidates (60%),
- the utility values from Kovacs 2021.

1.5.18 Overall worst case

The overall worst-case scenario analysis combined all the assumptions least favourable to medical management. These assumptions were:

- the higher cost for surgery (£16,152)
- the higher average cost for assessment for resective epilepsy surgery (£13,178)
- 20% higher relapse rate for resective epilepsy surgery
- a lower proportion of people were eligible surgery candidates (26%)
- people do not discontinue ASMs
- the time horizon was 15 years
- utility values from the previous guideline model

1.6 Model validation

The model was developed in consultation with the committee; model structure, inputs and results were presented to and discussed with the committee for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model was peer reviewed by a second experienced health economist from the NGC; this included systematic checking of the model calculations.

1.7 Estimation of cost effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with 2 alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$ Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A	Cost effective if: • ICER < Threshold

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1.8 Interpreting results

NICE sets out the principles that committees should consider when judging whether an intervention offers good value for money.[23, 25, 26] In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated the alternative (that is, it was both less costly in terms of resource use and more clinically effective), or
- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the alternative.

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2 Results

2.1 Base case analysis

The total cost for surgery was higher compared to medical management (£56,204 compared to £31,627). A breakdown of the costs is presented in Table 17. The difference in cost is mostly driven by the cost of assessment for resective surgery and the procedure costs, which amounts to £30,942 in the base case scenario. Additional costs for surgery are also observed in the form of reoperation costs and complication costs. However, resective epilepsy surgery also generates savings downstream by reducing the number of appointment costs, admission costs, and anti-seizure medication costs because more people obtain seizure freedom in the surgery arm.

Table 17: Cost breakdown per patient (probabilistic)

	Surgery	Medical management	Surgery minus Medical management
Assessment for resective surgery	£20,774	£0	£20,774
Surgery	£10,168	£0	£10,168
Appointment costs	£3,563	£5,409	-£1,847
Anti-seizure medication costs	£13,976	£19,277	-£5,300
Admissions	£3,244	£6,941	-£3,697
Reoperations	£676	£0	£676
Complications	£3,802	£0	£3,802
Total costs	£56,204	£31,627	£24,577

The mean QALYs were considerably higher for surgery (15.91 compared to 13.76). The base case results indicated surgery was cost effective at NICE's £20,000 threshold with a cost per QALY of £11,425.

Table 18: 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 scatterplot in Figure 5 shows the base case results of the probabilistic analysis. Almost all the points lie in the north-east quadrant and 96.5% of them are below the NICE threshold line of £20,000 per QALY gained.

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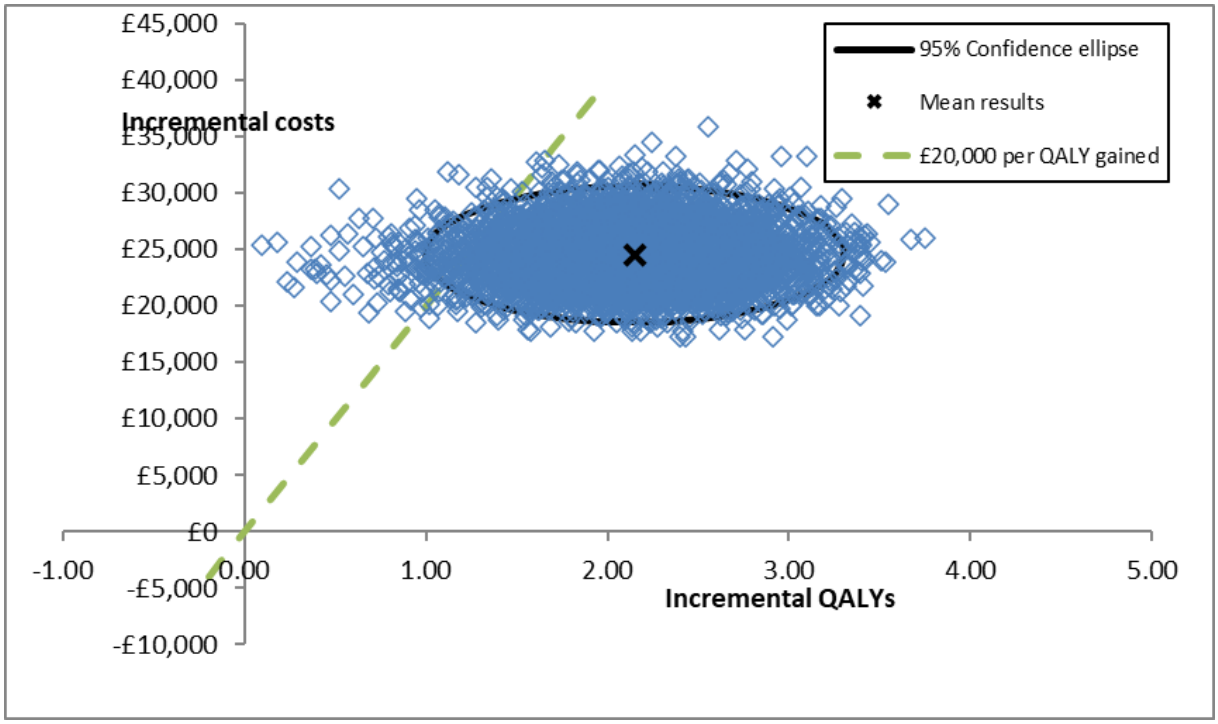
Figure 5: Base case cost effectiveness of surgery versus medical management: scatterplot of 5,000 probabilistic iterations on the cost effectiveness plane



2.2 Sensitivity analyses

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 19. Only when all the most pessimistic assumptions were made did the cost per QALY gained exceed £30,000 per QALY gained.

Table 19: One-way sensitivity analysis (deterministic)

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

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Scenario	Incremental costs	Incremental QALYs	Incremental cost per QALY gained
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

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3 Discussion

3.1 Summary of results

An original cost-utility analysis found that resective epilepsy surgery in adults is cost effective compared to medical management for treating drug refractory epilepsy (£11,425 per QALY gained). This study was assessed as directly applicable with minor limitations.

Resective epilepsy surgery in adults with drug refractory epilepsy has 96.5% probability of being cost effective at NICE's £20,000 threshold and a 99.3% probability of being cost effective at NICE's £30,000 threshold.

3.2 Limitations and interpretation

A limitation with this analysis is that the treatment effect on seizure is based on only two RCTs with small patient numbers. However, these one-year outcomes do seem to correlate well with the one-year outcome of observational studies. The trials followed up patients for a maximum of two years, so for the model the longer-term outcomes were calculated using observational cohort studies with between 5 and 15 years of follow-up. A sensitivity analysis was conducted using a 15-year time horizon. In this sensitivity 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 for most patients.

Different studies have produced different utility values for seizure free and non-seizure-free health states. The model used a study that was relatively large and in a UK population. The results were a little sensitive to the utility values used but even under the most conservative assumption, surgery still cost less than £20,000 per QALY gained.

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.

In most long-term outcome studies (including de Tisi 2011) assessing the effectiveness of epilepsy surgery, seizure freedom was defined as being completely seizure free or with only simple partial seizures, now referred to as 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.

Another limitation with this cost effectiveness analysis is that resource use was partly based on committee opinion. The committee were confident in their estimates but acknowledged published data is preferable for estimating resource use.

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3.3 Assessment of people for surgery

Assessing people to see if they could be treated by surgery is necessary but resource intensive. Indeed, it was the most significant cost in our analysis. The survey we conducted of 10 adult surgical centres suggested that there was great variability in:

- The cost of preoperative assessment (using standard unit costs) per patient assessed (£5,474 to £13,178)
- The proportion of patients that go on to surgery (26% to 60%).

It is not possible to deduce whether some centres are more efficient than others, since there will be considerable variation in case load and also some tests might not have been picked up from the case notes in some centres. Furthermore, although the total sample size is substantial, the number of patients per centre ranged from 35-100. However, there is enough variability to suggest some uncertainty about the cost of assessment.

The number of preoperative assessment tests required per person will be dependent on how easily the epileptic zone is identified. In current practice the cost of assessment for resective epilepsy surgery for people where the epileptic zone is more easily identified would likely fall in between the lower cost scenario and the average cost calculated for the base case (£5,474 – £8,182). Conversely, for people where the epileptic zone is more difficult to identify the cost for assessment for resective epilepsy surgery would likely fall between the average cost used in the base case and the higher cost used for the scenario analysis (£8,182 - £13,178), although it will be higher for those few people undergoing the most complex preoperative assessments. The committee acknowledged that in instances where the epileptic zone is more difficult to identify, post-surgery outcomes may not be as good as in those where the epileptogenic zone was more clearly defined. In a sensitivity analysis where the relapse rate in the surgery arm was 20% higher the cost per QALY was £12,608. In addition, when the preoperative assessment costs were higher, the cost per QALY gained was £16,827. Therefore, the committee concluded that epilepsy surgery would likely be cost effective for those people undergoing very complex assessments for resective epilepsy surgery.

When the probability of going on to have surgery was higher (60%) the cost per QALY was £8,174 and when the probability of being a surgery candidate was lower (26%) the cost per QALY was £16,537. The committee noted that in current practice adults with drug refractory epilepsy were not always referred for resective epilepsy surgery assessment because it can sometimes be seen as a ‘last resort’ option once a large number of ASMs have been tried. The committee acknowledged that referring more people with drug refectory epilepsy for resective epilepsy surgery assessment may change the proportion of people for whom surgery is suitable. However, they noted the proportion of people receiving resective epilepsy surgery would be, unlikely to be less than 26%, thus indicating the overall cost effectiveness of the results would not change substantially if more people were referred.

3.4 Generalisability to other populations or settings

Insufficient data were available to model the cost effectiveness of resective epilepsy surgery in a paediatric population. However, the committee discussed how the results of the adult epilepsy model may translate into a paediatric population.

The committee acknowledged that the cost of preoperative assessment 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.[19, 20] There is also some evidence that if seizure free they are more likely to be able to stop taking anti-seizure medication,[19, 20] which would be a cost saving in the longer term. For children there is evidence of improved cognitive development in children.[5, 38-40] In addition, drug refractory

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children who are not seizure free may have more outpatient appointments than adults. The committee noted that other data inputs in the model would likely be similar to adults except that additional reoperations may arise in children in the longer term once they reach adulthood, although this is only for a small proportion of people. Therefore, because the sensitivity analysis assuming higher assessment for resective surgery costs still demonstrated surgery was a cost-effective strategy (£16,827 per QALY gained), the committee concluded resective epilepsy surgery in children is highly likely to be cost effective.

This cost effectiveness analysis is taken from a UK NHS setting. The model used NHS reference costs and the cost effectiveness of resective epilepsy surgery was assessed using NICE's £20,000 threshold. Therefore, the results of this cost effectiveness may not be transferable to other countries or settings.

3.5 Comparisons with published studies

Two studies assessing the cost effectiveness of different preoperative assessment strategies were identified and included in the epilepsy surgery review.

Burch 2012[6] found that fluorodeoxyglucose positron emission tomography (fdgPET) and subsequent surgery in appropriate patients was cost effective compared to medical management (£1,671 per QALY gained). The addition of intracranial electroencephalography to fdgPET was also cost effective (£1,925 per QALY gained).

Kovacs 2021[6]found that the use of subdural grid electrodes and stereoelectroencephalography followed by surgery in appropriate patients were cost effective compared to medical management (ICER: £2,802 per QALY gained and £4,284 per QALY gained respectively).

Neither of these economic evaluations captured the RCT evidence identified in the guideline's clinical review and our original health economic analysis used different utility values. Our economic evaluation did however use Kovacs 2021 utility values in a scenario analysis. Because Burch 2012 is a UK Health Technology Assessment resources for costs were similar (for example, costs for surgery were taken from NHS reference costs). Kovacs 2021 was an economic analysis from a Hungarian health care perspective and so costs may not be directly comparable due to differences in health care settings.

In addition, as part of our original health economic analysis we conducted a survey of surgical centres to assess the total cost of preoperative assessment for those that go on to have surgery and those that continue with medical management. This probably explains why a higher cost per QALY gained was observed in our original economic analysis.

Our original economic analysis employed a similar long-term model structure to Burch 2012 whereby health states were used to model seizure freedom. However, this structure differed from Kovacs 2021 where health states were not used, and outcomes were evaluated for different types of epilepsy surgery (temporal lobe resection and extratemporal lobe resection). Standardised mortality ratios in our analysis were adapted from the same sources as those employed in both Burch 2012 and Kovacs 2021.

3.6 Conclusions

From this analysis, resective epilepsy surgery appears to be cost effective for adults with drug refractory epilepsy. The model used a mixture of trial evidence, observational studies a bespoke survey of surgical centres, and expert opinion. The committee felt this was a robust analysis that would allow them to strongly recommend resective epilepsy surgery in both adults and children with drug resistant epilepsy.

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