

Epilepsies in children, young people and adults

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

NICE guideline <number>

Economic analysis report

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1 Methods

1.1 Model overview

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

1.1.1 Comparators

9 The following comparators were included in the analysis:

- 10 1. Resective epilepsy surgery
- 11 2. Medical management

12 In clinical practice there are a number of different types of resective epilepsy surgery people
13 can receive. However, in adults, the most common type is temporal lobe resection. The
14 committee wanted to incorporate all types of epilepsy surgery in this cost effectiveness
15 analysis so conclusions could be made regarding the cost effectiveness of epilepsy surgery
16 in general. The RCTs included in the clinical review which were used to inform the short-
17 term outcomes of our health economic model assessed the effectiveness of temporal lobe
18 resection. The long-term effectiveness data for epilepsy surgery was taken from de Tisi
19 2011¹¹. In that study, 81% of people received anterior temporal lobe resection, 7% of people
20 received a temporal lesionectomy, 3% of people received extratemporal lesionectomy, 3% of
21 people received extratemporal lobe resection, 2% of people received a hemispherectomy,
22 and 1% of people received epilepsy surgical resection as part of palliative care. The
23 committee noted that the proportion of people undergoing each type of surgical procedure
24 was reflective of what was observed in UK clinical practice. However, the cost effectiveness
25 of each specific type of surgical procedure, is not estimable from this model because the
26 model parameters (seizure outcomes, utilities, and costs) are not well defined for specific
27 procedures. Furthermore, the type of surgical procedure that will be suitable will only be
28 apparent after preoperative assessment has taken place. Given the magnitude of the cost of
29 assessment, it is appropriate to evaluate surgery in general, at the point of referral for
30 assessment.

1.1.2 Population

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

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

1.2 Approach to modelling

42 A two-part model was developed which included a decision tree to model post-procedural
43 outcomes (over 1 year) followed by a Markov model for the estimation of long-term outcomes
44 and costs.

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

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

5 The decision tree model only captures immediate consequences of the intervention as
6 reported by the randomised trials, which was seizure freedom at 1 year^{13, 44} and for one trial
7 2 years¹³. In order to estimate costs and outcomes beyond the period of 1 year, a Markov
8 model was developed for each comparator using data from two long-term outcome studies:

- 9 • One long-term study reported outcomes for people after epilepsy surgery¹¹ and
- 10 • an additional long-term study reported outcomes for people with drug-refractory epilepsy
11 receiving medical management⁸.

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

1.2.1 Model structure

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

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

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

40

Figure 1: Model structure – decision tree

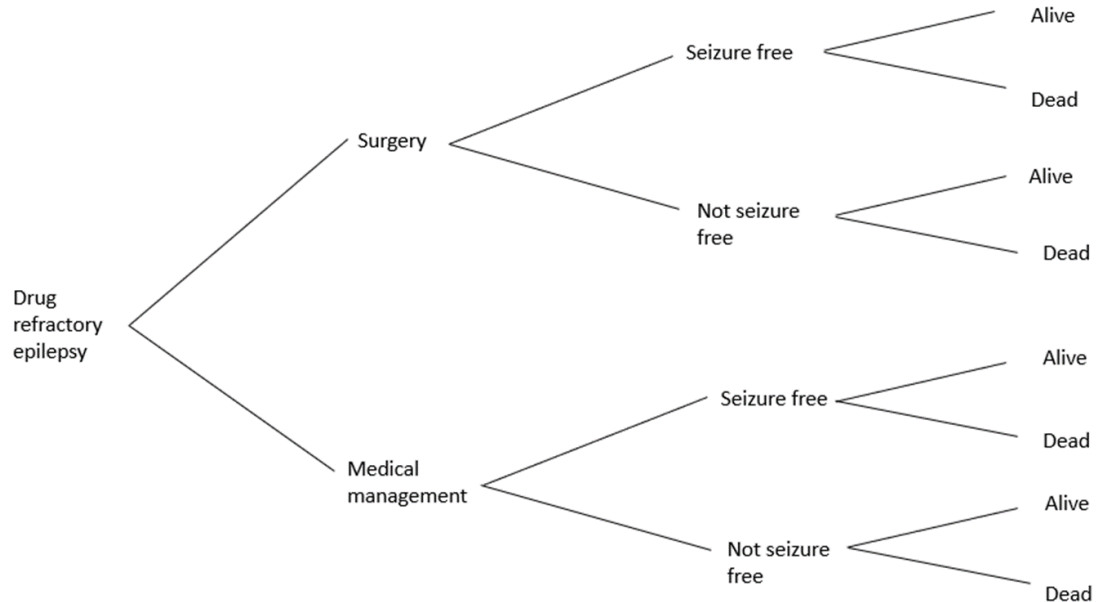


Figure 2 represents the long-term structure of the model. After one-year, patients enter into the Markov model in the health state they finished in the decision tree. For both resective epilepsy surgery and continued medical management, patients can enter the Markov model, being seizure free, having 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.

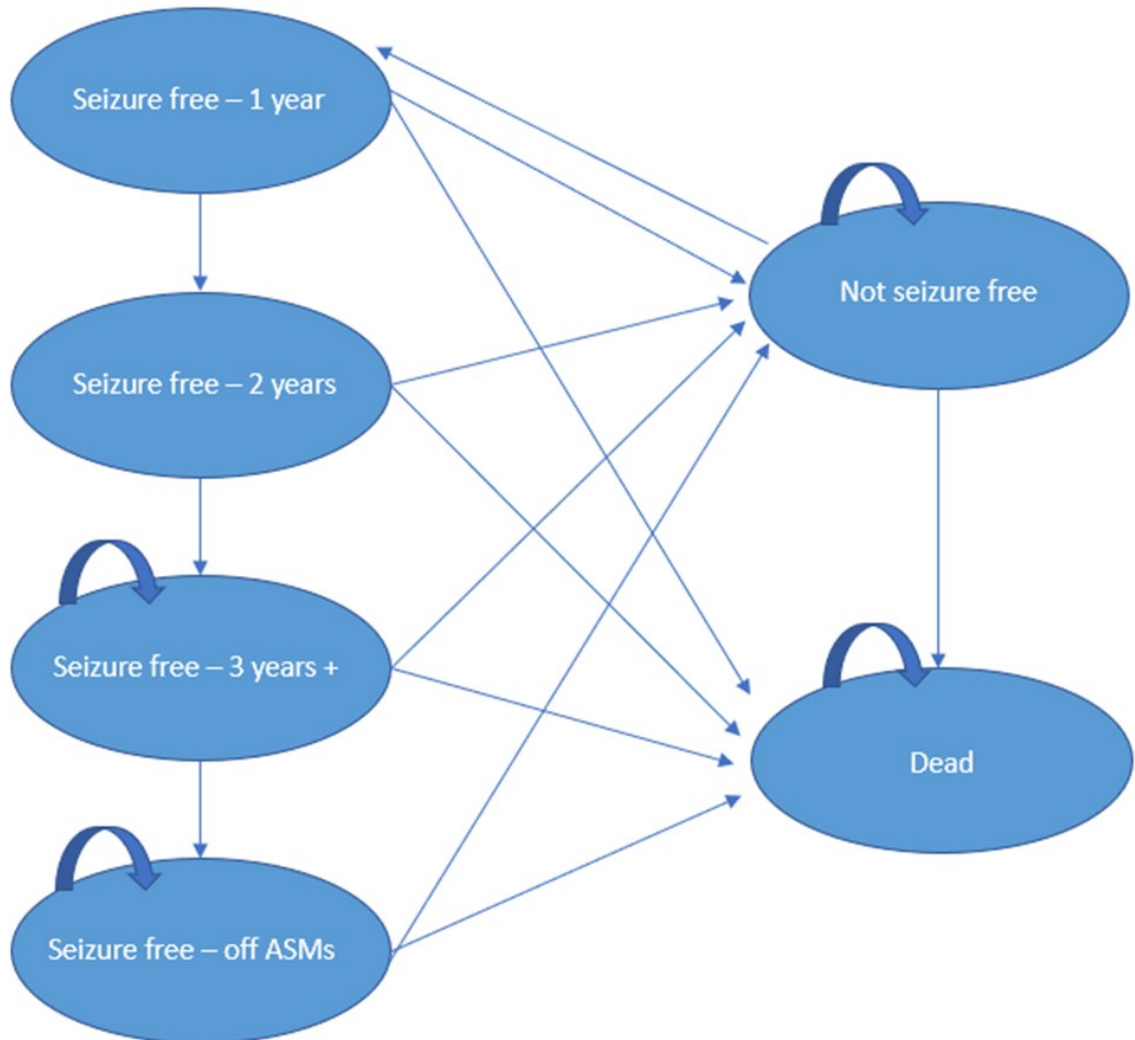
The Markov model has four tunnel states, seizure free for one year, seizure free for two years, seizure free for three or more years, and seizure free and off Anti-Seizure Medications (ASMs). Tunnel states add memory into the Markov model relaxing the Markovian assumption. In the four tunnel states patients 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 state, 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.

Figure 2: Model structure – Markov model

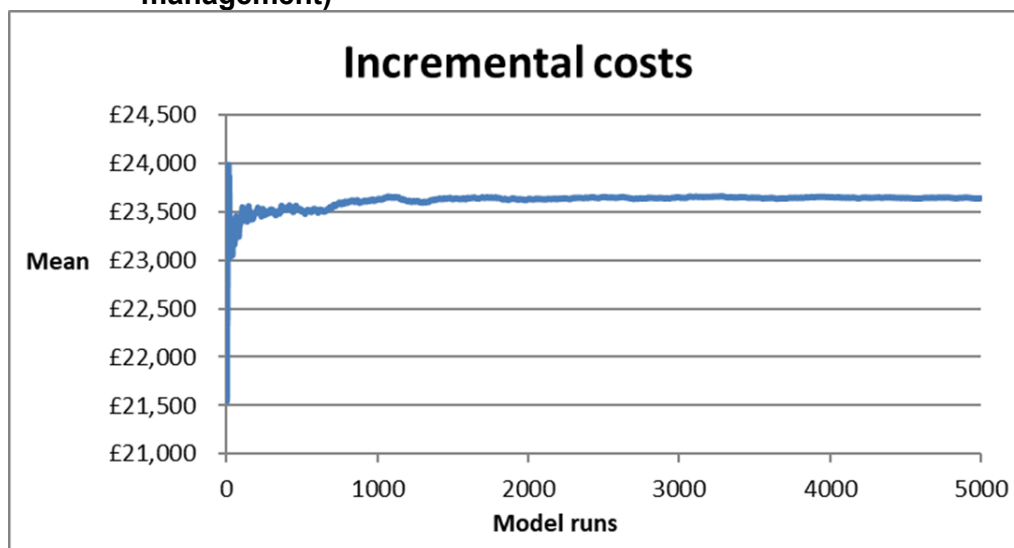


1.2.2 Uncertainty

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

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

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



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

8 **Table 1: Description of the type and properties of distributions used in the**
 9 **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: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • Mean = $\ln(\text{mean cost}) - SE^2/2$ • SE = $[\ln(\text{upper 95\% CI}) - \ln(\text{lower 95\% CI})]/(1.96 \times 2)$ $\sqrt{\ln \frac{SE^2 + \text{mean}^2}{\text{mean}^2}}$ 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: <ul style="list-style-type: none"> • Alpha = $(\text{mean}/SE)^2$ • Beta = SE^2/Mean

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

- 1 The following variables were left deterministic (that is, they were not varied in the
 2 probabilistic analysis):
- 3 • the cost-effectiveness threshold
 - 4 • the probability of discontinuing Anti-seizure Medication (ASM)
 - 5 • probability of reoperation
 - 6 • probability of long-term complications from resective epilepsy surgery
 - 7 • the proportion of people obtaining a $\geq 50\%$ reduction in seizures and a $< 50\%$ reduction in
 8 seizures
 - 9 • appointment costs
 - 10 • admission costs
 - 11 • ASM costs

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

1.3 Model inputs

1.3.1 Summary table of model inputs

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

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

Input	Data	Source	Probability distribution
Comparators	<ul style="list-style-type: none"> • 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			

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 \geq 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

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

- 1 Abbreviations: A&E = Accident & Emergency, ASMs = Anti-seizure medications, MM = Medical management,
 2 SMR = Standardised mortality ratio
- 3 (a) The committee discussed the probability of long-term complications post-surgery and referred to a 2013
 4 systematic literature review¹⁴ where the probability of major complications from surgery was 4.7%. The
 5 committee did however note that the probability of long-term complications from resective epilepsy surgery is
 6 decreasing, making reference to a more recent 2021 publication³.
- 7 (b) Weighted to account for a proportion of people reported in de Tisi 2011 who were not completely seizure free
 8 and still experienced simple partial seizures, now referred to as focal aware seizures (FAS). 82% of people in
 9 de Tisi 2011 were completely seizure free at end of follow-up. The SMR for seizure free was applied for these
 10 82% of people and the SMR for not seizure free was applied to the remaining 18% of people who were not
 11 completely seizure free
- 12 (c) In Väättäinen 2020 the utility values were reported for people with a $\geq 50\%$ reduction and seizures and a
 13 $< 50\%$ reduction seizures so the proportion of people achieving a $\geq 50\%$ reduction and seizures and a $< 50\%$
 14 reduction seizures was weighted by values reported in Neligan 2011²⁷
- 15 (d) A beta distribution was applied to the cumulative probability at 5 years and the probabilistic probability at 5
 16 years was converted to a rate and an annual probability
- 17 (e) A Gamma distribution was used because the probabilistic utility values were calculated to maintain rank.
 18 Utility decrements were calculated, and a Gamma distribution was applied to these utility decrements.
- 19 (f) The committee estimated the cost of long-term complications to be £5,000: cognitive deficits would not incur
 20 a cost to the NHS and major visual field defects would incur a small cost to the NHS. Stroke (and
 21 haemorrhage) would lead to the most significant costs to the NHS. A stroke may incur high initial costs of
 22 rehabilitation but these high costs are unlikely to be continuous for the majority of people.

1.3.2 Initial cohort settings

2 The starting age for people in the model was 35. The average age of people in the model
 3 was based on the larger RCT⁴⁴ included in the clinical review, assessing the effectiveness of
 4 surgery in adults. In Wiebe 2001⁴⁴ there were 40 people in each arm of the trial (surgery
 5 versus medical therapy whilst waiting for surgery). The average age of people in the surgery
 6 arm was 35.5 and the average age of people in the medical management arm was 34.4. In
 7 Engel 2012¹³ there were 15 people in the surgery arm and 23 people in the medical
 8 management arm. The average age of people in the surgery arm was 37.5 and the average
 9 age of people in the medical management arm was 30.9.

10 The proportion of males in the model was 46.7%. This value was obtained from de Tisi
 11 2011¹¹ which informed the long-term outcomes for resective epilepsy surgery to be used in
 12 the cost effectiveness analysis.

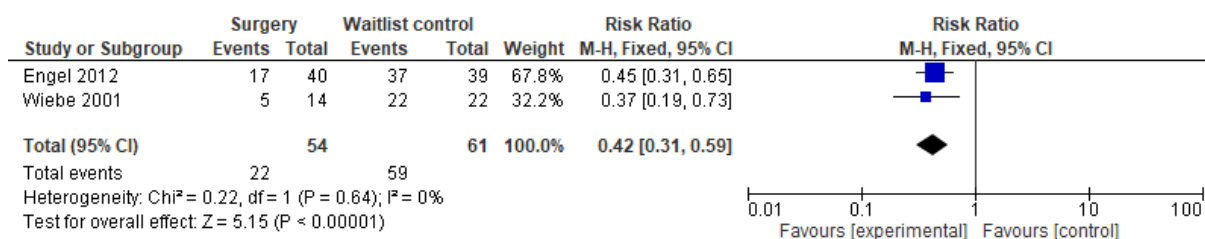
1.3.3 Short-term outcomes

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

1.3.3.7 Probability of having seizures

18 The probability of seizures for people receiving medical management was estimated using
 19 data included in the clinical review^{13, 44}.

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



21

22

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

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

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

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

1.3.3.2 Probability of mortality for the surgery arm

2 Mortality for the first year after resective epilepsy surgery (including operative mortality) was
3 estimated from de Tisi 2011¹¹. Various data inputs were sourced for operative mortality^{7, 12, 15,}
4 ^{17, 21, 32-35, 37, 42} however these studies only provided data on the risk of operative mortality and
5 did not provide data for all-cause mortality within 1-year after surgery. Conversely, mortality
6 reported in de Tisi 2011¹¹ included operative mortality as well as mortality from other causes.
7 Therefore, because de Tisi¹¹ was used to inform the long-term outcomes of epilepsy surgery
8 in our health economic analysis this was deemed the most appropriate value to use.

9 In de Tisi 2011¹¹ 5 people of the of 649 people in the total cohort died within 1 year of
10 surgery. This resulted in a probability of 0.77% for mortality within one year after resective
11 epilepsy surgery.

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

1.3.3.3 Probability of mortality for medical management arm

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

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

$$18 \quad p_{mortality\ MM} = (p_{NSF\ MM} * p_{mortality\ NSF\ MM}) + p_{mortality\ SF\ MM} * (1 - p_{NSF\ MM})$$

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

21 This resulted in the probability of mortality at year 1 in the medical management arm of
22 0.39%.

23 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

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

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

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

- 32 • Stroke (including haemorrhage)
- 33 • Visual field defect
- 34 • Cognitive defect

35 The committee discussed that the probability of long-term complications after resective
36 epilepsy surgery are rare, and in recent years have become increasingly rarer. The
37 committee made reference to a systematic literature review published in 2013¹⁴ which noted
38 4.7% of patients had a major neurological complication after resective epilepsy surgery, with
39 the most common major long-term complication being a visual field defect (2.1%). The
40 committee also noted a more recent publication from 2021³ which illustrates long-term
41 complications from resective epilepsy surgery are now rarer. Therefore, the committee
42 concluded the probability of a long-term complication of 4.0% would be an appropriate value
43 to use and might be an overestimate.

1.3.3.5 Longer-term outcomes

2 Transition probabilities were calculated for the risk of relapse and remission for both medical
 3 management and surgery. This risk of relapse is defined as the probability of transitioning
 4 from seizure free to not seizure free and the risk of remission is defined as the probability of
 5 transitioning from not seizure free to seizure free. The probability of relapse and remission for
 6 people undergoing epilepsy surgery was estimated based on values reported in de Tisi
 7 2011¹¹ and the probability of relapse and remission for medical management was estimated
 8 based on values reported in Callaghan 2011⁸.

1.3.3.6 Probability of relapse and remission for surgery

10 de Tisi 2011¹¹ is UK prospective cohort study of 615 adults undergoing resective epilepsy
 11 surgery. The number of people relapsing and entering remission after surgery was presented
 12 in a graph (Figure 3) which provided a breakdown of the number of people in four distinct
 13 categories. These categories are presented in Table 3.

14 **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

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

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

24 **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%

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%

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

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

10 **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%

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

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

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

1.3.3.7 Probability of relapse and remission for medical management

2 The probability of relapse and remission for medical management was based on values
3 reported in Callaghan 2011⁸. They reported values of remission and relapse for up to 5 years
4 for a cohort of 246 patients followed prospectively at a single epilepsy centre in the USA.

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

$$10 \quad r = \frac{-\ln(1 - p)}{t}$$

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

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

$$14 \quad p = 1 - \exp(-rt)$$

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

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

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

1.3.3.8 Discontinuation of Anti-Seizure Medications

22 If people had been seizure free for three or more years, then they had an annual probability
23 of 15.7% for discontinuing their Anti-Seizure Medication (ASM). This probability was obtained
24 from Wieser 2003⁴⁵.

1.3.3.9 Probability of reoperation

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

1.3.4 Life expectancy

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

- 36 • Risk of death associated with epilepsy surgery
- 37 • Standardised mortality ratios (SMRs) for seizure free (surgery and medical
38 management) and not seizure free were applied to the general population mortality
39 rates from Office of National Statistic (ONS) life tables³¹

40 Mortality in the first year after surgery was estimated based on values reported in de Tisi
41 2011¹¹ as outlined in section 1.3.3.2. The risk of surgical mortality was also incorporated into

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

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

9 $Death\ Rate_{SF\ Surgery} = Death\ Rate_{general\ population} * SMR_{SF\ surgery}$

10 $Death\ Rate_{SF\ Medical\ Management} = Death\ Rate_{general\ population} * SMR_{SF\ medical\ management}$

11 $Death\ Rate_{NSF} = Death\ Rate_{general\ population} * SMR_{NSF}$

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

14 $p = 1 - exp(-r)$

15 Where p is the probability and r is the rate.

16 The SMR for seizure free was obtained from Salanova 2002³⁶. This study was one of the two
17 studies used to obtain the pooled SMR for seizure free in Choi 2008⁹. Choi 2008⁹ was the
18 study used to model the long-term outcomes in the Health Technology Assessment (HTA)
19 which was included in the epilepsy surgery evidence review. The pooled SMR from Choi
20 2008⁹ was also used in Kovacs 2021¹⁸ which was the other included health economic study
21 in the epilepsy surgery review.

22 Salanova 2002³⁶ estimated the SMR for people who are seizure free to be 1.78. Sperling
23 1999⁴¹ was the additional study used to obtain the pooled SMR in Choi 2008 which
24 estimated the number of deaths to be 0. Therefore, the overall pooled SMR reported in Choi
25 2008⁹ was 1.11. The committee noted that the inclusion of a study that had no deaths might
26 lead to the SMR being under-estimated. Therefore, they concluded that it would be more
27 appropriate to use the SMR of 1.78 reported in Salanova 2002³⁶ in the base case analysis
28 and use the pooled SMR reported in Choi 2008⁹ in a sensitivity analysis. Details of this
29 sensitivity analysis can be found in 1.5.7.

30 de Tisi 2011¹¹ was the long-term outcome study used to inform the long-term outcomes after
31 epilepsy surgery. However, seizure freedom in de Tisi 2011¹¹ was defined as either
32 completely seizure free or seizure free except for simple partial seizures (now termed focal
33 aware seizures, FAS). Conversely, Callaghan 2011⁸, which was used to inform the long-term
34 outcomes of medical management, defined seizure freedom as completely seizure free.
35 Therefore, an adjustment to the SMR for people who were seizure free in the surgery arm
36 was applied to account for the number of people who were seizure free in the surgery arm
37 who were not completely seizure free (i.e., a proportion of people still experienced focal
38 aware seizures). It was calculated from de Tisi 2011¹¹ that 82% of people at the end of
39 follow-up were completely seizure free. Therefore, the SMR for people seizure free surgery
40 in the surgery arm in the following way:

41 $SMR_{seizure\ free\ surgery} = (SMR_{seizure\ free} * 0.82) + (SMR_{not\ seizure\ free} * (1 - 0.82))$

42 SMRs for not seizure free for surgery and medical management were also reported in Choi
43 2008⁹. The SMR reported in Choi 2008⁹ for not seizure free surgery was 5.64 and the SMR
44 for not seizure free medical management was 5.40. The SMR for not seizure free surgery
45 was calculated by pooling two SMRs together^{36, 41} and the SMR for not seizure free surgery

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

3 The resulting SMRs applied to the general population mortality rates are presented in Table
 4 6.

5 **Table 6: Standardised mortality ratios**

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

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

1.3.5 Utilities

8 Utilities for people who are seizure free and not seizure free were based on values from
 9 Väättäinen 2020⁴³. The values cited in Väättäinen 2020⁴³ were based on EQ-5D data from the
 10 SANAD study. These utility values were also used in the health economic model assessing
 11 the cost effectiveness of different ASMs developed for this guideline. The utility values
 12 reported in Väättäinen 2020 are reported in Table 7.

13 **Table 7: Utility values reported in Väättäinen 2020**

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

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

15 Because the utility values reported in Väättäinen 2020⁴³ provide utility values for people
 16 experiencing a ≥50% reduction in seizures and <50% reduction in seizures, data were
 17 required to calculate the utility for the not seizure free health state in our health economic
 18 model. Neligan 2011²⁷ reported the number of people in a drug refractory cohort of 139
 19 people receiving medical management in the UK who achieved seizure freedom, a 50% -
 20 99% improvement in seizures and <50% improvement in seizures. At the end of follow-up,
 21 41 people experienced a ≥50% reduction in seizures and 72 people experienced a <50%
 22 reduction in seizures. Therefore, of the 139 people in the cohort study, 29.50% of people
 23 experienced a ≥50% reduction in seizures and 51.80% of people experienced a <50%
 24 reduction in seizures.

25 Therefore, of the people that were not seizure free $29.50\% / [29.50\% + 51.80\%] = 36.28\%$
 26 experienced a ≥50% reduction in seizures. These proportions were applied to the utility for a
 27 ≥50% reduction in seizures and the utility for a <50% reduction in seizures to obtain the
 28 utility for not seizure free – see Table 7.

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

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

$$4 \quad Utility_{seizure\ free\ surgery} = (utility_{seizure\ free} * 0.82) + (utility_{not\ seizure\ free} * (1 - 0.82))$$

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

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

9 The utility of seizure freedom in the surgery arm was calculated by combining the utility value
 10 for seizure free and the utility value for not seizure free reported in Table 7, using the formula
 11 outlined above. The utility values used in the health economic analysis for not seizure free for
 12 medical management and surgery are the values calculated by weighting the proportion of
 13 people achieving a $\geq 50\%$ reduction in seizures and a $< 50\%$ reduction in seizures reported
 14 by the utility values reported in Väättäinen 2020⁴³ (see Table 7).

15 To make these utility values, probabilistic utility decrements between states were calculated
 16 using the data from Väättäinen 2020⁴³.

17 The utility decrements are reported in Table 8.

18 **Table 8: Utility decrements for the utility values reported in Väättäinen 2020**

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

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

21 Probabilistic values were then calculated for the utility decrements using a Gamma
 22 distribution. The resulting probabilistic values for the utility values reported in Väättäinen
 23 2020⁴³ were calculated in the following way:

- 24 • The probabilistic utility value for seizure free was calculated by subtracting
 25 probabilistic Decrement 1 from the utility value for full health (i.e., 1).
- 26 • The probabilistic utility values for a $\geq 50\%$ reduction in seizures was calculated by
 27 subtracting the probabilistic Decrement 2 from the probabilistic utility value for seizure
 28 free.
- 29 • The probabilistic utility value for a $< 50\%$ reduction in seizures was calculated by
 30 subtracting the probabilistic Decrement 3 from the probabilistic utility value for a
 31 $\geq 50\%$ reduction in seizures.

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

1 A utility decrement of 0.2 for long term complications associated with resective epilepsy
 2 surgery was also applied to the model. This utility decrement was obtained from Choi 2008⁹.

1.3.6 Assessment for resective epilepsy surgery survey

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

6 A survey was administered to participating adult epilepsy surgery centres to obtain the
 7 average number of tests for people undergoing assessment for resective epilepsy surgery.
 8 Ten surgical centres submitted data, all of which were used in the economic analysis.. Out of
 9 the ten surgical centres who submitted data, data was available for a total of 762patients.

10 Overall, fourteen epilepsy surgical centres were contacted resulting in a response rate of
 11 71%. The committee were provided a list of the participating surgical centres and concluded
 12 the data would provide a representative sample to obtain the resource use for preoperative
 13 assessment.

14 The average number of tests for all participating centres was calculated by summing the total
 15 number of people receiving a given test across all participating centres and dividing this by
 16 the total cohort of people. The unit cost for each respective test was then multiplied by the
 17 average number of tests to obtain the average cost of each test for a person undergoing
 18 assessment for resective epilepsy surgery.

19 **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

20 All sources for unit costs were taken from NHS reference costs 2019/20²⁹ if available. The exceptions were:
 21 (a) The committee concluded the same cost for MRI as reported in NHS reference costs could be used for
 22 fMRI
 23 (b) A committee member provided the cost from their centre
 24 (c) The committee estimated the cost to be between £2,000 and £5,500 so the average of these estimates
 25 was used

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

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

1.3.6.7 Probability of receiving epilepsy surgery

8 The centres were also asked about the outcome of patients being assessed for surgery to
 9 assess what proportion go on to have it. The probability of being a surgery candidate was
 10 estimated to be 41.3%. The numerator of this probability only included those people who
 11 were eligible for resective epilepsy surgery and surgery went ahead or was due to take
 12 place. In other words, the numerator did not include those people who were eligible for
 13 surgery but did not consent to surgery. In the model we add the test of costing those
 14 patients that didn't go on to have surgery as well as the cost of the surgical patient
 15 themselves. So, the total assessment cost per patient undergoing surgery is £8,182 +
 16 £11,628 = £19,809, where £11,628 = £8,182 * (58.7%) / 41.3%.

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

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

1.3.7 Other resource use and costs

1.3.7.1 Surgery

26 The cost of surgery was calculated taking the weighted average of the total costs divided by
 27 the total number of Finished Consultant Episodes (FCE's). The total number of FCE's was
 28 9,087 and the sum of the national average was £95,552,533. The total cost of surgery used
 29 in the health economic model was £10,185 (£95,552,533/9,087). The costs used in the
 30 calculation for the total cost of surgery are presented in Table 10.

31 **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

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

1 Source: NHS reference costs 2019/20 ²⁹

1.3.7.2 Surgery complications

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

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

17 The long-term cost of complications from surgery was assumed to be £5,000 per year over
 18 the lifetime. This cost was based on committee opinion. The committee noted it was
 19 challenging to estimate the cost of long-term complications but noted an annual cost of
 20 £5,000 applied across a lifetime horizon would likely be an overestimate.

1.3.7.3 Appointments

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

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

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

3 Data on the probability of service use was taken from Jacoby 1998¹⁶ or based on committee
 4 opinion. Resource use from Jacoby and 1998¹⁶ was multiplied by an expected number of
 5 contacts estimated by the committee. Jacoby and colleagues collected data for three groups
 6 of patients, those experiencing no seizures, less than one seizure a month, and more than
 7 one seizure a month. Our health economic analysis only has two health states where costs
 8 and utilities are applied (seizure free and not seizure free) and the not seizure free health
 9 state does not differentiate between people experiencing less than one seizure a month and
 10 more than one seizure a month. Overall, the difference between service use for people
 11 experiencing less than one seizure a month and more than one seizure a month reported in
 12 Jacoby 1998¹⁶ was relatively small. Therefore, the service use associated with experiencing
 13 more than one seizure per month is used in the model for all people who are not seizure free.
 14 Unit costs and resource use summarised in Table 11.

15 **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

16 Sources:

17 (a) NHS reference costs 2019/20²⁹

18 (b) PSSRU 2020, GP consultation (9.22 minutes), including qualification costs and direct care costs¹⁰

19 (c) Committee opinion

20 (d) Jacoby 1998¹⁶

1.3.24 Admissions

22 As outlined in section 1.3.7.3, data on the probability of service use was taken from Jacoby
 23 1998¹⁶ and multiplied by an expected number of contacts estimated by the committee. The
 24 costs for admissions are presented in Table 12.

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

	Probability of use			Unit cost (d)	Cost (£)	
	Seizure free (a)	Not seizure free (b)	Expected number of visits given non-zero use (c)		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

26 Sources:

- 1 (a) Annual probability of accessing a service if seizure free, from Jacoby 1998¹⁶
 2 (b) Annual probability of accessing a seizure if experiencing one seizure per month, from Jacoby 1998¹⁶
 3 (c) Committee opinion and previous guideline ²⁴
 4 (d) NHS references costs 2019/20²⁹

1.3.7.5 Drugs

6 It was assumed patients in the model would receive on average 2.5 ASMs a day. Some
 7 people could discontinue ASMs if they have been seizure free for 3 or more years – see
 8 1.3.3.8.

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

21 **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

22 Sources:

- 23 (a) Committee opinion
 24 (b) Committee opinion and the British National Formulary (BNF)⁴
 25 (c) BNF⁴, Date accessed: 16/05/21

26 The total average cost for one ASM was calculated to be £417. This figure was multiplied by
 27 2.5 to obtain the total yearly costs for ASMs per person (£1,042).

1.4 Computations

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

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

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

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

14 Discounting formula:

$$\text{Discounted total} = \frac{\text{Total}}{(1+r)^n}$$

Where:

r =discount rate per annum
 n =time (years)

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

1.5 Sensitivity analyses

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

- 22 1. Utilities assuming 50% of people in the surgery arm have a $\geq 50\%$ reduction in
- 23 seizures
- 24 2. Utilities from Kovacs 2021
- 25 3. Utilities from the previous NICE guideline
- 26 4. The probability of receiving surgery is higher
- 27 5. The probability of receiving surgery is lower
- 28 6. Treatment effects from Wiebe 2001 only
- 29 7. SMR for seizure free is 1.11
- 30 8. Surgery relapse rate higher
- 31 9. Surgery relapse rate lower
- 32 10. Pre-surgical evaluation costs higher
- 33 11. Pre-surgical evaluation costs lower
- 34 12. Surgery cost higher
- 35 13. Surgery cost lower
- 36 14. Time horizon 15 years
- 37 15. No discontinuation of ASMs
- 38 16. Overall best case
- 39 17. Overall worst case

1.5.1 Utilities assuming 50% of people in the surgery arm have a $\geq 50\%$ 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 $\geq 50\%$ reduction in seizures and a $< 50\%$ reduction in seizures reported in Neligan 2011²⁷ by the utility values reported in Väättäinen 2020⁴³. Because Neligan 2011²⁷ provided data on the proportion of people who achieved a $\geq 50\%$ 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 $\geq 50\%$ 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 $\geq 50\%$ 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 2021¹⁸ 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 (Väättäinen 2020) were 0.869, 0.805, and 0.623 for seizure free, a $\geq 50\%$ reduction in seizures, and $< 50\%$ reduction in seizures respectively.

The utility values used in the previous NICE guideline model²⁴ assessing the cost effectiveness of different ASMs for monotherapy and add-on therapy had a smaller utility difference compared to those reported in Väättäinen 2020⁴³. 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 Väättäinen 2020⁴³.

It is not clear why the utility values from the previous NICE guideline model are quite different but the ones from Väättäinen 2020⁴³ 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.

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

5 **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

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

1.5.4 The probability of receiving surgery is higher

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

1.5.5 The probability of receiving surgery is lower

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

1.5.6 Treatment effects from Wiebe 2001 only

19 In the base case analysis the probability of not being seizure free in the surgery arm was
 20 estimated using both studies included in the clinical review^{13, 44}. However, a sensitivity
 21 analysis was conducted using the treatment effects from Wiebe 2001. This is because Engel
 22 2012 was a smaller RCT compared to Wiebe 2001 due to the trial terminating early due to
 23 poor recruitment.

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

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

1.5.7 SMR for seizure free is lower

32 As outlined in section 1.3.4 the pooled SMR reported in Choi 2008⁹ was 1.11. This was used
 33 in the sensitivity analysis. However, the committee concluded it would be more appropriate to
 34 use the SMR of 1.78 reported in Salanova 2002³⁶ in the base case because the other study⁴¹
 35 which was used to obtain the pooled SMR reported in Choi 2008⁹ reported zero deaths.

1.5.8 Surgery relapse rate higher

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

1.5.9 Surgery relapse rate lower

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

1.5.10 Assessment for resective epilepsy costs higher

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

1.5.11 Assessment for resective epilepsy costs lower

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

1.5.12 Surgery costs higher

- 11 A sensitivity analysis was conducted assuming a higher total cost for epilepsy surgery.
12 This cost was calculated by estimating the total average weighted cost for complex
13 intracranial procedures (AA50A – AA50C), which was £16,152.

1.5.13 Surgery costs lower

- 15 A sensitivity analysis was conducted assuming a higher total cost for epilepsy surgery.
16 This cost was calculated by estimating the weighted average cost for major intracranial
17 procedures (AA53A – AA53D), which was £8,376.

1.5.14 Time horizon 15 years

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

1.5.15 No discontinuation of anti-seizure medication

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

1.5.16 Overall best case

- 29 The overall best-case scenario analysis combined all the assumptions most favourable to
30 resective epilepsy surgery. These assumptions were:
- 31 • the lower cost for surgery (£8,376)
 - 32 • the lower average cost for assessment for resective epilepsy surgery (£5,474)
 - 33 • 20% lower relapse rate for resective epilepsy surgery
 - 34 • the standardised mortality ratio for seizure free was 1.11
 - 35 • a higher proportion of people were eligible surgery candidates (60%),
 - 36 • the utility values from Kovacs 2021.

1.5.17 Overall worst case

- 2 The overall worst-case scenario analysis combined all the assumptions least favourable to
3 medical management. These assumptions were:
- 4 • the higher cost for surgery (£16,152)
 - 5 • the higher average cost for assessment for resective epilepsy surgery (£13,178)
 - 6 • 20% higher relapse rate for resective epilepsy surgery
 - 7 • a lower proportion of people were eligible surgery candidates (26%)
 - 8 • people do not discontinue ASMs
 - 9 • the time horizon was 15 years
 - 10 • utility values from the previous guideline model

1.6 Model validation

- 12 The model was developed in consultation with the committee; model structure, inputs and
13 results were presented to and discussed with the committee for clinical validation and
14 interpretation.
- 15 The model was systematically checked by the health economist undertaking the analysis;
16 this included inputting null and extreme values and checking that results were plausible given
17 inputs. The model was peer reviewed by a second experienced health economist from the
18 NGC; this included systematic checking of the model calculations.

1.7 Estimation of cost effectiveness

- 20 The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER).
21 This is calculated by dividing the difference in costs associated with 2 alternatives by the
22 difference in QALYs. The decision rule then applied is that if the ICER falls below a given
23 cost per QALY threshold the result is considered to be cost effective. If both costs are lower
24 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

1.8 Interpreting results

- 26 NICE sets out the principles that committees should consider when judging whether an
27 intervention offers good value for money.^{23, 25, 26} In general, an intervention was considered
28 to be cost effective if either of the following criteria applied (given that the estimate was
29 considered plausible):
- 30 • The intervention dominated the alternative (that is, it was both less costly in terms of
31 resource use and more clinically effective), or
 - 32 • The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained
33 compared with the alternative.
- 34

2 Results

2.1 Base case analysis

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

11 **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

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

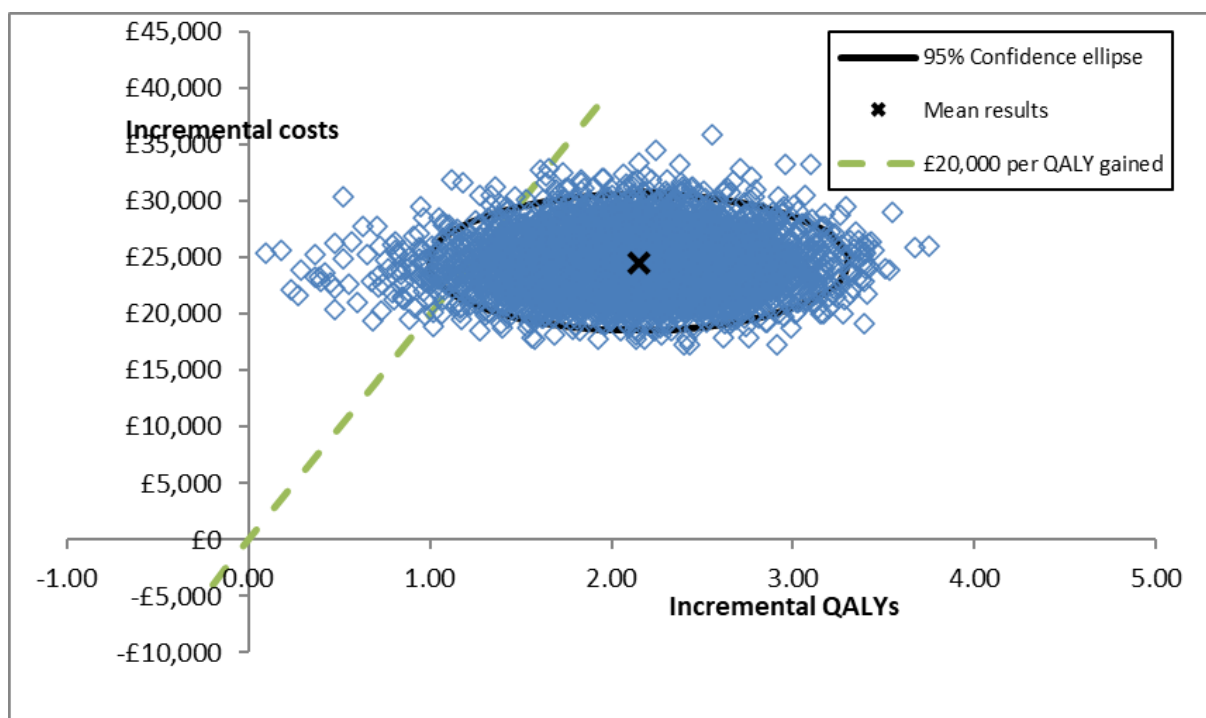
15 **Table 18: Base case cost effectiveness results (probabilistic)**

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%	

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

19

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



3
4

2.2 Sensitivity analyses

6 The sensitivity analyses showed that the results were a little sensitive to the utility values,
 7 and costs, but only when the time horizon was lowered (to 15 years) did the cost per QALY
 8 gained exceed the £20,000 per QALY gained threshold - Table 19. Only when all the most
 9 pessimistic assumptions were made did the cost per QALY gained exceed £30,000 per
 10 QALY gained.

11 **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 $\geq 50\%$ 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

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
Overall best case	£9,931	3.53	£2,811
Overall worst case	£66,725	0.37	£182,331

1

3 Discussion

3.1 Summary of results

- 3 An original cost-utility analysis found that resective epilepsy surgery in adults is cost effective
4 compared to medical management for treating drug refractory epilepsy (£11,425 per QALY
5 gained). This study was assessed as directly applicable with minor limitations.
- 6 Resective epilepsy surgery in adults with drug refractory epilepsy has 96.5% probability of
7 being cost effective at NICE's £20,000 threshold and a 99.3% probability of being cost
8 effective at NICE's £30,000 threshold.

3.2 Limitations and interpretation

- 10 A limitation with this analysis is that the treatment effect on seizure is based on only two
11 RCTs with small patient numbers. However, these one-year outcomes do seem to correlate
12 well with the one-year outcome of observational studies. The trials followed up patients for a
13 maximum of two years, so for the model the longer-term outcomes were calculated using
14 observational cohort studies with between 5 and 15 years of follow-up. A sensitivity analysis
15 was conducted using a 15-year time horizon. In this sensitivity analysis the cost per QALY
16 gained was £28,231, which is above NICE's £20,000 threshold but below NICE's £30,000
17 threshold. However, the committee thought that this was conservative, and it is reasonable to
18 assume that the impact of surgery can continue for longer for most patients.
- 19 Different studies have produced different utility values for seizure free and non-seizure-free
20 health states. The model used a study that was relatively large and in a UK population. The
21 results were a little sensitive to the utility values used but even under the most conservative
22 assumption, surgery still cost less than £20,000 per QALY gained.
- 23 Callaghan 2011's definition of drug refractory epilepsy was stricter than the current definition
24 of drug refractory. Callaghan defined drug resistant epilepsy as people who had failed on at
25 least two antiseizure medications (ASMs) and were experiencing at least one seizure per
26 month. The current ILAE definition of drug refractory epilepsy is the occurrence of
27 uncontrolled seizures despite two tolerated and appropriately chosen ASMs. Therefore, the
28 cohort of people in Callaghan 2011 may have had more severe drug refractory epilepsy
29 compared to a drug resistant cohort as defined by the ILAE definition. The committee did
30 however note that the estimated proportion of people entering seizure freedom (5.6%) and
31 relapsing (22%) each year seemed reasonable.
- 32 In most long-term outcome studies (including de Tisi 2011) assessing the effectiveness of
33 epilepsy surgery, seizure freedom was defined as being completely seizure free or with only
34 simple partial seizures, now referred to as focal aware seizures (FAS). This is reasonable but
35 this definition did not correspond with the definition used in the trials or the studies that were
36 sourced for health state utility scores and standardised mortality ratios, which were only
37 people who were completely seizure-free. To overcome the challenges posed by these
38 differential definitions, adjustments were made to the standardised mortality ratios (SMRs)
39 and utilities for seizure freedom in the surgery arm using the proportion of people that
40 experienced FAS in de Tisi 2011. The utility and mortality for people experiencing only FAS
41 is not known, and so conservative assumptions were made, which if anything, might have
42 under-estimated the benefits of surgery but as only 18% of people of the seizure free sample
43 had experienced FAS, the committee concluded this would not alter the overall results of the
44 cost effectiveness analysis.
- 45 Another limitation with this cost effectiveness analysis is that resource use was partly based
46 on committee opinion. The committee were confident in their estimates but acknowledged
47 published data is preferable for estimating resource use.

3.3 Assessment of people for surgery

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

- 5 • The cost of preoperative assessment (using standard unit costs) per patient assessed
6 (£5,474 to £13,178)
- 7 • The proportion of patients that go on to surgery (26% to 60%).

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

13 The number of preoperative assessment tests required per person will be dependent on how
14 easily the epileptic zone is identified. In current practice the cost of assessment for resective
15 epilepsy surgery for people where the epileptic zone is more easily identified would likely fall
16 in between the lower cost scenario and the average cost calculated for the base case
17 (£5,474 – £8,182). Conversely, for people where the epileptic zone is more difficult to identify
18 the cost for assessment for resective epilepsy surgery would likely fall between the average
19 cost used in the base case and the higher cost used for the scenario analysis (£8,182 -
20 £13,178), although it will be higher for those few people undergoing the most complex
21 preoperative assessments. The committee acknowledged that in instances where the
22 epileptic zone is more difficult to identify, post-surgery outcomes may not be as good as in
23 those where the epileptogenic zone was more clearly defined. In a sensitivity analysis where
24 the relapse rate in the surgery arm was 20% higher the cost per QALY was £12,608. In
25 addition, when the preoperative assessment costs were higher, the cost per QALY gained
26 was £16,827. Therefore, the committee concluded that epilepsy surgery would likely be cost
27 effective for those people undergoing very complex assessments for resective epilepsy
28 surgery.

29 When the probability of going on to have surgery was higher (60%) the cost per QALY was
30 £8,174 and when the probability of being a surgery candidate was lower (26%) the cost per
31 QALY was £16,537. The committee noted that in current practice adults with drug refractory
32 epilepsy were not always referred for resective epilepsy surgery assessment because it can
33 sometimes be seen as a 'last resort' option once a large number of ASMs have been tried.
34 The committee acknowledged that referring more people with drug refractory epilepsy for
35 resective epilepsy surgery assessment may change the proportion of people for whom
36 surgery is suitable. However, they noted the proportion of people receiving resective epilepsy
37 surgery would be, unlikely to be less than 26%, thus indicating the overall cost effectiveness
38 of the results would not change substantially if more people were referred.

3.4 Generalisability to other populations or settings

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

43 The committee acknowledged that the cost of preoperative assessment may be more
44 expensive for children as they might require additional tests. However, the committee noted
45 seizure freedom after resective epilepsy surgery might be more likely in children than adults
46 and the benefits for children could be accrued over a longer period.^{19, 20} There is also some
47 evidence that if seizure free they are more likely to be able to stop taking anti-seizure
48 medication,^{19, 20} which would be a cost saving in the longer term. For children there is
49 evidence of improved cognitive development in children.^{5, 38-40} In addition, drug refractory

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

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

3.5 Comparisons with published studies

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

16 Burch 2012⁶ found that fluorodeoxyglucose positron emission tomography (fdgPET) and
17 subsequent surgery in appropriate patients was cost effective compared to medical
18 management (£1,671 per QALY gained). The addition of intracranial electroencephalography
19 to fdgPET was also cost effective (£1,925 per QALY gained).

20 Kovacs 2021⁶ found that the use of subdural grid electrodes and
21 stereoelectroencephalography followed by surgery in appropriate patients were cost effective
22 compared to medical management (ICER: £2,802 per QALY gained and £4,284 per QALY
23 gained respectively).

24 Neither of these economic evaluations captured the RCT evidence identified in the
25 guideline's clinical review and our original health economic analysis used different utility
26 values. Our economic evaluation did however use Kovacs 2021 utility values in a scenario
27 analysis. Because Burch 2012 is a UK Health Technology Assessment resources for costs
28 were similar (for example, costs for surgery were taken from NHS reference costs). Kovacs
29 2021 was an economic analysis from a Hungarian health care perspective and so costs may
30 not be directly comparable due to differences in health care settings.

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

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

3.6 Conclusions

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

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