TITLE PAGE

Title: Is resective surgery cost-effective for adults with epilepsy?

- **A cost-utility analysis in a publicly funded healthcare system**

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ABSTRACT

Background: Resective epilepsy surgery is an established clinical intervention, but the cost effectiveness at a national healthcare level is uncertain. This study evaluates the cost effectiveness of resective epilepsy surgery compared to medical management in adults from national healthcare and personal social services perspectives.

Methods: A de-novo decision analytic model was developed – comprising of a one-year decision tree and life-time Markov model to evaluate life-time costs and Quality Adjusted Life Years (QALYs). Data were obtained from UK epilepsy surgery centres to evaluate the costs of pre-operative assessment and the probability of undergoing resection after pre-surgical evaluation. Other clinical inputs were obtained from a systematic literature review. The main outcome of the analysis was the incremental cost-effectiveness ratio (ICER) – with a cost-effectiveness threshold set at £20,000 cost per QALY gained.

Results: Data from 762 patients informed pre-operative evaluation costs and the probability of undergoing epilepsy surgery post pre-surgical evaluation. The total lifetime cost of epilepsy treatment for people that had surgical treatment was £56,911, compared with £32,490 for medical management. Total QALYs per person for surgery were 15.91 and 13.76 for medical management. Resective epilepsy surgery was shown to be cost effective with an ICER of £11,348 per QALY gained.

Conclusions: Our data inform and strengthen recommendations to prioritise referral of those with drug refractory epilepsy to surgical centres. We provide a health economic rationale for development and support of resective epilepsy surgery programs across national healthcare systems.

KEY MESSAGES

What is already known on the topic?

Considering a nationwide healthcare system perspective, a single study has been published in a European context supporting the economic rationale of resective epilepsy surgery. That work, though, evaluates the economic rationale without including the costs of presurgical evaluation if a patient is deemed inoperable after pre-surgical evaluation.

What this study adds

Our study provides evidence of cost-effectiveness from a total healthcare perspective rather than only considering cost-effectiveness in people who have already been fully assessed as operable. Evaluating the cost-effectiveness of resective epilepsy surgery from the point of referral to epilepsy surgery programmes is reflective of treatment pathways in clinical practice. Although the costs of pre-surgical evaluation for surgery can be high, and not all people referred for epilepsy surgery will be suitable candidates for resection, funding a national epilepsy surgery program is cost effective.

How this study might affect research, practice or policy

Resective epilepsy surgery for drug resistant epilepsy is cost-effective, even when including assessment of people who are subsequently found not to be appropriate for operative intervention. The study provides increased support for referral to epilepsy surgery programs.

Glossary of terms

Decision tree: A type of health economic model structure used to evaluate different strategies or interventions. Decision trees are typically used to evaluate short-term outcomes.

Deterministic analysis: used in models where outcomes are precisely determined by inputs.

Direct costs: Expenses directly associated with medical treatment, such as hospital stays, medications, and procedures.

Cost-effective: An intervention that provides a good value for its cost, often measured by the cost per unit of health benefit. The cost-effectiveness threshold in our analysis is £20,000 per QALY gained.

Cost-utility analysis: A method that compares the cost of an intervention to its health outcomes measured using Quality Adjusted Life Years (QALYs).

Half-cycle correction: An adjustment in a Markov model to account for the fact that transitions between health states occur continuously rather than at discrete intervals.

Healthcare costs: The total expenses associated with medical care, including direct, indirect, and intangible costs.

Incremental cost-effectiveness ratio (ICER): A statistic used to summarize the cost-effectiveness of a health intervention, calculated as the difference in cost divided by the difference in effectiveness between two interventions. Effectiveness in our analysis was measured using QALYs.

Indirect costs: Costs related to lost productivity, time, and other non-medical expenses due to illness or treatment.

Markov model: A mathematical model used to represent transitions between different health states over time.

Mean costs: The average cost of an intervention or treatment across a population.

Mean QALYs: The average Quality Adjusted Life Years gained from an intervention across a population.

Monte Carlo simulation: A computational technique that uses random sampling to estimate the probability distribution of outcomes in a model.

One-way sensitivity analysis: A method to assess how the results of a model change when one parameter is varied while others are held constant.

Probabilistic sensitivity analysis (PSA): A technique that evaluates the uncertainty in a model by varying multiple parameters simultaneously according to their probability distributions.

Probability distribution: A mathematical function that describes the likelihood of different outcomes in a random process.

Quality Adjusted Life Years (QALYs): A measure of the value of health outcomes, combining both the quantity and quality of life gained from an intervention.

Unit cost: The cost per single unit of service or intervention.

Utility: A measure of the preference or value that individuals place on different health outcomes ranging from 0 – 1, where 1 represents full health and 0 represents dead.

INTRODUCTION

Drug refractory epilepsy (DRE) results in increased morbidity, premature mortality,[1] and accounts for approximately 80% of healthcare costs in epilepsy care.[2] Direct costs include ongoing trials of anti-seizure medications (ASMs) - around 50% of the total cost[3,4] - and hospitalisations owing to recurrent seizures or injuries. Indirect costs of epilepsy, such as unemployment and adverse impacts from comorbidities, are several-fold greater than the direct care costs.[5]

Epilepsy surgery has established clinical effectiveness for adults,[6–8] with up to 58% of treated individuals achieving seizure freedom.[8] Despite recommended early referral for epilepsy surgery,[9,10] there is marked under-utilisation across healthcare settings.[11–13] Over 10 million people globally are potential surgery candidates,[14] yet even in high-income countries only an estimated 1% of appropriate people are evaluated.[15]

While previous analyses have suggested that epilepsy surgery is cost effective,[16–18] these studies have relied on single centre data, [19–24] or only evaluated people who proceeded to resection.[25] Owing to their alternative models of fees and costs, economic analyses conducted from single private healthcare centres may have limited applicability for publicly funded national healthcare systems. [19–22,24] To comprehensively address the cost effectiveness of epilepsy surgery in a government-funded health care system, a model was developed over a life-time horizon, estimating quality-adjusted life years (QALYs) and health service costs for all adults referred to resective epilepsy surgical programmes.

METHODS

Our model was developed as part of the National Institute of Health and Care Excellence (NICE) Guideline on Epilepsies in children, young people and adults; NG217 published in 2022.[26] Conceptualisation and sourcing of data inputs was conducted in 2021, prior to guideline publication. The NG217 Committee consisted of UK-based experts in epilepsy, epilepsy surgeons, neuropsychologists, pharmacists, and people with lived experience of epilepsy (online supplemental 1). As part of the guideline, a detailed health economic plan was developed. **A brief online version of the plan can be found on the NICE website (https://www.nice.org.uk/process/pmg36/chapter/economic-evaluation-2#measuring-and-valuing-health-effects-in-cost-utility-analyses).** Model structure, inputs and results were iteratively discussed with the guideline committee for clinical validation and interpretation.[26] In instances where no data were identified, committee estimates were used to populate the model. **The model was developed using Microsoft Excel and Visual Basic for Applications.**

Model structure

We developed a decision analytic model comparing resective epilepsy surgery to medical management (MM) in adults from a United Kingdom National Health Service (NHS) perspective. A healthcare perspective was chosen, aligning to the NICE reference case for assessing cost-effectiveness.

A cohort of adults with epilepsy was initially followed in the model through a one-year decision tree (Figure 1). For the surgical arm, the decision tree modelled the costs and effects of pre-operative assessment and resective epilepsy surgery. The cost of pre-operative evaluation was included for those people who underwent resective epilepsy surgery and for

those who underwent pre-operative evaluation but did not progress to resective epilepsy surgery (i.e., continued to receive MM). The MM arm modelled the cost and effects for one year of MM for people with drug refractory focal epilepsy **– including the costs and outcomes for those who underwent pre-surgical evaluation but did not proceed to surgery**. At the end of one-year, proportions of the cohort were seizure free, not seizure free, or dead.

Long-term outcomes were modelled by 49 one-year Markov cycles (covering ages 36 to 85 years; Figure 2). The states of the Markov model were 'seizure free for one year', 'seizure free for two years', 'seizure free for three or more years', 'seizure free off ASMs', 'not seizure free', and 'dead'. Within a one-year cycle, people were attributed an annual probability of remaining in their current health state, dying, or transitioning to 'seizure free' or 'not seizure free' – dependent on their original health state. Time-dependency was incorporated to track how long people were seizure free, and to capture the probability of discontinuing ASMs once seizure freedom was obtained.

Model inputs

The probability of obtaining seizure freedom in year one was derived from two randomised controlled trials (RCTs)[7,8] identified in the clinical review conducted as part of the guideline update.[26] The starting age of the model cohort was 35 years – aligned with the average age of people included in the larger RCT.[8] The proportion of males in the model was 46.7%. This proportion was obtained from the long-term outcome study for resective epilepsy surgery,[27] as this study reported on a significantly larger cohort size in comparison to the rest of our outcome data and was based on UK outcomes. The probability of surgical mortality was also obtained from this dataset.[27] Probability of a permanent complication resulting from resective

epilepsy surgery was set at 4.0%.[28–31] Data inputs for the one-year decision tree are presented in Table 1.

Table 1: Economic model data inputs

Model inputs: clinical outcomes. MM=medical management. ASM=anti-seizure medication. SMR=standardised mortality ratios. LnRR=log response ratio, SE=standard error, NA=not applicable.

Data input	Base case value	Probability distribution
One year decision tree outcomes		
Probability of 'not being seizure free' in the MM arm	96.7% [7,8]	Beta (Alpha: 59, Beta: 2)
Risk ratio	0.42 [7,8]	Lognormal (LnRR: -0.87, SE: 0.16)
Probability of mortality in the surgery arm	0.77% [27]	Beta (Alpha: 5, Beta: 644)
Probability of long-term complication from resective epilepsy surgery	4.0% [28–31]	NA
Long-term Markov model outcomes		
Annual probability of remission surgery	Various annual probabilities (see online supplemental 2) [27]	Beta
Annual probability of relapse surgery	Various annual probabilities (see online supplemental 2) [27]	Beta
Annual probability of remission MM	5.6% [32]	Beta (Alpha: 62, Beta: 184)
Annual probability of relapse MM	22.0% [32]	Beta (Alpha: 42, Beta: 17)
Annual probability of discontinuing ASMs each year $\geq$ 3 years of seizure freedom	15.7% [33]	NA
Probability of reoperation	4.0% (Committee assumption)	NA
SMR 'seizure free' surgery	2.42 (see online supplemental 3)	Made probabilistic based on the probability distributions applied for the SMR of seizure free MM and the SMR of not seizure free.
SMR 'seizure free' MM	1.78 [34]	Lognormal LnRR = 0.575, SE = 0.678
SMR 'not seizure free'	5.40 [28–31]	Lognormal LnRR = 1.686, SE = 0.158
Utility value – 'Seizure free' surgery'	0.858 [27,35]	See online supplemental 4
Utility value – 'Seizure free' medical management	0.869 [35]	See online supplemental 4
Utility value – 'Not seizure free'	0.689 [35,36]	See online supplemental 4
Utility decrement – annual decrement for long-term complications of surgery	**0.2 [28–31]**	**NA**
Utility value - Dead	**0**	**NA**

Owing to an absence of long-term RCT data relating to epilepsy surgery, outcomes for surgery and MM were obtained from two long-term observational studies (Table 1).[27,32] Transition probabilities were calculated for the risk of relapse (transitioning from 'seizure free' to 'not seizure free') and remission (transitioning from 'not seizure free' to 'seizure free'). Annual probabilities for relapse and remission in the MM arm were calculated from the cumulative probabilities previously reported, [32] assuming a constant rate of remission and relapse over the five-year period. Transition probabilities in the surgical arm were calculated differently to those in the MM arm because annual data were available for the number of people entering remission and relapsing (up to year 15). These data were used to calculate individual annual probabilities up to year 15 and were subsequently extrapolated beyond this for the remainder of a person's lifetime (online supplemental 2). The committee assumed a lifetime 4% probability of re-operation.

Standardised Mortality Ratios (SMRs) for 'seizure free' and 'not seizure free' individuals were applied to the general population mortality rates.[37] The SMR for 'not seizure free' and 'seizure free' MM were obtained from published estimates.[28–31,34] The SMR for 'seizure free' following epilepsy surgery was adjusted to account for the differing definitions of seizure freedom in our two long-term outcome studies (online supplemental 3).[27,32]

Health state utilities (Table 1) were based on reported values for people who were 'seizure free'; 'people experiencing a ≥50% reduction in seizures'; and 'people experiencing a <50% reduction in seizures'.[35] The utility for 'seizure free' in the surgical arm was adjusted to account for different definitions of seizure freedom (online supplemental 4). To obtain a utility value for 'not seizure free', data on the proportion of people experiencing a ≥50%

reduction in seizures, and people experiencing a <50% reduction in seizures,[36] were multiplied by published utility values.[35] A yearly utility decrement of 0.2 was applied for those who experienced long term complications from surgery.

Pre-operative assessment resource use for individuals undergoing pre-surgical evaluation were collected from adult surgical centres in England and Wales using a standardised data capture form (online supplemental 5). Each centre recorded data for a minimum of 50 consecutive patients who had completed surgical work-up **between the start of 2018 and the end of 2019. It was thought inappropriate to sample data in 2020 or 2021 as epilepsy care was severely affected by the COVID-19 pandemic.** Data were anonymised and aggregately analysed to obtain the mean number of pre-surgical evaluation tests per patient. The cost of pre-surgical evaluation was calculated by multiplying the mean number of tests by the unit cost and summing these (online supplemental 6).

Unit costs used in the model were obtained from NHS-specific published sources.[38,39] Costs for amytal testing, magnetoencephalography and electrocorticography were obtained from the participating centres that provided these tests. A number of costs used in the model are updated here and so differ slightly from those published in the NICE guideline (online supplemental 7).[36]

Potential adverse consequences of epilepsy surgery include immediate complications such as infection or haemorrhage, which can usually be treated promptly and often have no long-term sequalae. Also, there are small risks of stroke and mortality. The average long-term cost of surgical complications, this encompassing all potential surgical complications, was taken to

be £5,000 per year over a lifetime horizon. This figure was thought likely an over-estimate by the NICE Committee, but retained to avoid positive bias in the model.

The cost of outpatient contacts included the cost of an initial neurology appointment, subsequent neurology appointments and primary care consultations (online supplemental 6). In-patient and emergency admission costs were also included in the analysis (online supplemental 6). Probability of service use for the costs of outpatient contacts and admissions was obtained from previous literature,[40] and informed by expert committee opinion. The NICE committee estimated the proportion of people who would receive each ASM and assumed people with drug resistant epilepsy would receive an average of 2.5 ASMs. The total annual cost of ASMs per person was calculated to be £1,082 (online supplemental 6). The cost of the resective operation itself was £10,185.[38]

Analysis

To calculate overall cost effectiveness, costs and QALYs for each cycle were calculated by multiplying the proportion of the cohort in each state by the corresponding cost or utility, with a half-cycle correction applied. Costs and QALYs were discounted at 3.5% to reflect time preference –in line with the NICE reference case. Costs and QALYs were summed across the lifetime horizon (50 years). The incremental cost-effectiveness ratio (ICER) was calculated by dividing the difference in total costs for surgery and MM by the difference in QALYs.

The model was run probabilistically using Monte Carlo simulation (10,000 times) to account for the uncertainty around input parameters. A probability distribution was defined for most model inputs. For each simulation, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were re-calculated using these values. Main results of the model are presented probabilistically. One-way sensitivity analyses are presented deterministically.

For the probabilistic analysis a beta distribution was applied to the following data inputs: probability of not being seizure free for MM, probability of mortality in the surgery arm, probability of relapse and remission for surgery and MM, and the probability of being a surgery candidate. A gamma or beta distribution was applied to the average number of pre-surgical evaluation tests. The distribution applied was dependent on the usage of each specific test. When the average resource use per person was above one, a beta distribution was applied – a gamma distribution was applied to remaining tests (online supplemental 6). A gamma distribution was applied to the cost of surgery and the utility values used in our model (online supplemental 4). A log-normal distribution was applied to the risk ratio for seizures at one year (surgery versus waiting list) and the SMRs (Table 1).

A total of 18 deterministic one-way sensitivity analyses were conducted (online supplemental 7). These included using utilities from different sources; altering the costs for surgery and pre-surgical evaluation; employing a 15-year time horizon; assuming people did not discontinue their ASMs once they obtained seizure freedom; and assuming a higher cost for pre-surgical investigations.

The model was systematically checked by the health economist undertaking the analysis (AB); this included inputting null and extreme values to check that results were plausible. The calculations were systematically checked by a second experienced health economist (DW). The model was made available to registered stakeholders of the guideline during public consultation.

RESULTS

Fourteen epilepsy surgical centres were contacted and ten provided data for a total of 762 adult individuals (online supplemental 8). The mean number of preoperative evaluation tests per person and corresponding unit costs for each test are presented in online supplemental 6. The average cost of preoperative assessment was £8,182 per person.

The proportion of people undergoing resective epilepsy surgery, having completed preoperative evaluation, was 41.3% (315/762). This included people who were eligible for resective epilepsy surgery and for whom surgery went ahead or was due to take place. People who were eligible for surgery but did not consent to surgery are not captured in this group.

For the probabilistic base case results, the total cost per person for surgery was estimated to be £56,911, and the total cost for MM was £32,490 (Table 2). Total QALYs per person for surgery was 15.91 and MM 13.76. Overall, resective epilepsy surgery was found to be cost effective with an ICER of £11,348 per QALY gained (Table 2). Deterministic results are listed in online supplemental 9.

Table 2: Cost effectiveness results per person (probabilistic results).

QALY=Quality-adjusted life-years.

.	**Surgery**	**Medical management**	**Surgery minus medical management**
Assessment for resective surgery cost	£20,823	£0	£20,823
Resective surgery cost	£10,201	£0	£10,201
Outpatient appointment cost	£3,631	£5,517	-£1,887
Anti-seizure medication cost	£14,522	£20,022	-£5,500
Admission cost	£3,254	£6,951	-£3,697
Reoperation costs	£678	£0	£678
Complications cost	£3,804	£0	£3,804
All costs	£56,911	£32,490	£24,442
QALYs	15.91	13.76	2.15
Incremental cost per QALY gained			£11,348

The results of the probabilistic analysis are illustrated in Figure 3, where each of the 10,000 iterations is plotted. Resective epilepsy surgery had a 97.0% probability of being cost effective at NICE's threshold of £20,000 per QALY gained (indicated by the proportion of iterations to the right of the dotted line). There was a 99.5% probability of surgery being cost effective at NICE's upper threshold of £30,000 per QALY gained (not shown in graph).

In all deterministic sensitivity analyses, resective surgery was cost effective at NICE's £20,000 threshold per QALY, apart from when the time horizon was reduced to 15 years (ICER: £28,093) and when the overall worst-case scenario was employed (online supplemental 9). The overall worst-case scenario comprised of all the scenarios tested in the one-way sensitivity analyses that favour MM to surgery (online supplemental 7). This sensitivity analysis was conducted to test these assumptions, but the NICE committee noted

that the overall worst-case scenario was highly unlikely to be representative of clinical practice.

A one-way sensitivity analysis was undertaken assuming the highest cost of pre-surgical evaluation across all ten surgical centres (£13,178 compared to £8,182) – illustrating that surgery remained cost-effective with an ICER of £16,679 per QALY gained. Another sensitivity analysis incorporated a higher cost for stereo-EEG (sEEG). This analysis assumed that 60% of people undergoing sEEG received standard sEEG (the NHS reference cost used in the base case analysis [£14,638]) and 40% of people received a more complex sEEG (£39,577; costs obtained from two participating surgical centres). This resulted in a mean cost for sEEG of £24,613. The results of this analysis indicated that epilepsy surgery was still cost-effective at £12,889 per QALY gained. Results of all 18 deterministic one-way sensitivity analyses are provided in online supplemental 9.

An analysis was also conducted altering the probability of receiving surgery post pre-surgical evaluation. When the probability of receiving surgery is higher (60%), the ICER was £8,042 per QALY gained and when the probability of receiving surgery is lower (26%), the ICER was £16,389 per QALY gained.

DISCUSSION

The clinical effectiveness of epilepsy surgery is established in appropriately selected cases. Despite this, resective surgery for people with drug resistant epilepsy is under-utilised.[6–8,11–13] Scarce budgets drive the need for cost-effectiveness analyses to support and expand epilepsy surgery programs.[41] Analysis of whether referral for epilepsy surgery is cost-effective, irrespective of whether a given individual proceeds to resection, is essential.

Our nationwide multicentre pre-surgical evaluation survey included costs of *all* adults referred for pre-surgical evaluation, thereby reflecting real-world costs of an epilepsy surgery program. We demonstrate epilepsy surgery for drug resistant epilepsy is cost effective, in 97.0% of simulations, at NICE's threshold of £20,000 per QALY gained. As such, this study provides a more definitive economic rationale for referral to epilepsy surgery programs. These data are broadly applicable to other **government-funded healthcare settings. The economic rationale for resective epilepsy surgery in low income to middle income healthcare countries requires specific consideration (online supplemental 10). It could be argued that the impetus for epilepsy surgery may be even greater in resource underprivileged settings, given the increased risk from seizures and the poor availability of ASMs.**

Pre-surgical evaluation itself is a significant proportion of the total cost of epilepsy surgery. 58.7% of people in our cohort who underwent pre-surgical evaluation did not proceed to resection. Prior studies have omitted this group when assessing the cost-effectiveness of epilepsy surgery (online supplemental 11).[22,25] Pre-surgical evaluation does, though, provide valuable insights to optimise patient care in those who do not proceed to surgery including uptake of alternative therapies, such as neuromodulation, and identification of psychogenic

non-epileptic/functional dissociative seizures. Capturing these potential benefits was not within the scope of our analysis. Similarly, indirect benefits from resection – for example the ability to return to the workforce, resume greater duties in the home and other factors improving socioeconomic productivity were not captured here **as these are not part of NICE Methodology. Benefit from epilepsy surgery would reduce indirect costs and thereby likely render epilepsy surgery even more cost effective**.

The cost of sEEG is variable depending on the complexities of a person's epilepsy. The cost of sEEG used in the base case analysis was obtained from NHS reference costs,[38] although the NICE committee acknowledged this cost may be an underestimate for more complex cases. Since model development, the frequency with which sEEG is used in pre-surgical evaluation has increased in addition to an increase in costs. The sensitivity analysis conducted assuming a higher cost for sEEG likely covers the increase in costs but does not account for the increased frequency with which sEEG is **deployed (please see online supplement 7). In our model, 20% of candidates received sEEG as part of their pre-surgical evaluation. A separate sensitivity analysis was conducted where it was assumed that the cost of pre-surgical evaluation was higher, using the highest total cost of pre-surgical evaluation across all participating centres (£13,178) – resulting in an ICER of £16,679 per QALY gained. In the sensitivity analysis where the cost of sEEG was increased, the cost of pre-surgical evaluation was £10,607 with an ICER of £12,889. Comparison of these analyses demonstrates that the total cost of pre-surgical evaluation / sEEG has scope to increase and still be cost-effective at NICE's £20,000 threshold. Further research is, though required to determine the ICER of surgery using frequencies of sEEG over and above 20% as well as more complex (higher cost) sEEG implantations.**

Utility values in our model were obtained from a non-drug refractory population owing to a lack of data in a drug-refractory cohort. Although, the utility values used in the model derive from a relatively large UK study, several sensitivity analyses were conducted using different utility values to assess this uncertainty. The results of these analyses indicated the model was potentially sensitive to the utility values used, but, even under the most conservative assumption, the ICER was less than £20,000 per QALY (online supplemental 9). The guideline committee discussed that drug-refractory specific utility values would likely increase the cost-effectiveness of epilepsy surgery owing to a greater utility difference between 'seizure free' and 'not seizure free'**. Those who have previously had drug resistant epilepsy may place a higher utility on seizure freedom compared to those in the non-drug refractory population. Also, those who are 'not seizure free' in a drug refractory cohort may be experiencing more severe or frequent seizures compared to those experiencing seizures in the non-drug refractory population.** Seizure frequency and severity were not measurable outcomes in our analysis. **These potential additional benefits from resective surgery could result in cost savings and a greater utility difference between surgery and MM, which would render surgery even more cost-effective.**

Paediatric cases were not included in our analysis. The logistical organisation for epilepsy surgery is different for children in the United Kingdom where resective epilepsy surgery is carried out at four designated Children's Epilepsy Surgery Service (CESS) Centres. There may be certain additional costs in children, for example the potential need for imaging to be performed under general anaesthesia. It is, though, inferred that epilepsy surgery is likely to be more cost effective in children, both in terms of direct and indirect costs as earlier control of seizures offers the prospect of earlier drug reduction better access to education and employment, greater social

mobility and decreased risk of mortality.[42] Similarly, it could be argued that for people younger than 35 years at the time of surgical resection (35 years being the entry-point for our model) cost effectiveness may be increased.

We also did not specifically explore stratification by learning ability. People with learning disabilities may require additional appointments, more time within appointments and specialist provision to undergo relevant testing (for example imaging and video-telemetry). This was difficult to capture here, although prospective evaluation for cost effectiveness of resective epilepsy surgery in people with learning disability may be worthwhile. The NICE Committee emphasised in their discussions that people with learning disability must not be excluded from epilepsy surgery programmes.

LIMITATIONS

There are several limitations to our study. Treatment effects in our analysis are based on two small RCTs, and therefore long-term outcomes were calculated using observational studies.[27,32] RCT evidence assessing the effectiveness of epilepsy surgery will likely always be short-term owing to ethical concerns associated with conducting longer-term RCTs – delaying epilepsy surgery when this is of proven benefit would not reflect clinical equipoise. One-year seizure freedom rates reported in the observational studies correlated well with the RCT data.

Owing to data availability at the time of model development, our long-term effectiveness data was based on two studies[27,32] – one for ascertaining the long-term effectiveness of surgery,[27] and the other for MM.[32] As the definition of seizure freedom differed in these studies, amendments were made to the surgery data to account for seizure freedom being inclusive of focal aware seizures (FAS; online supplement 2). The MM study employed a stricter definition of drug refractory epilepsy,[32,43] and therefore the model cohort may have had more severe drug refectory epilepsy. The committee however noted that reported relapse and remission values seemed compatible with current clinical practice. The long-term data for both studies was extrapolated differently (online supplement 2). In summary, data were extrapolated based on best fit. These values and the methodology were discussed with the guideline committee who concluded that the probability values correlated with UK clinical practice.

Utility values were obtained from a non-drug refractory population due to an absence of data for drug-refractory populations. Several sensitivity analyses were therefore conducted using different utility values. Analyses indicated the model was sensitive to utility values – but all ICERs were still less than £20,000 per QALY gained. Drug-refractory specific values would likely favour surgery due to a greater utility difference between health states.

Certain resource allocation assumptions were based on committee expertise (for example: cost of complications; probability of reoperation) or from centres who offered specific investigations. Owing to a lack of published data on the cost of fMRI, the committee assumed fMRI to be of the same cost as an MRI. The committee noted that this would likely result in an underestimation of the true fMRI cost but agreed that this assumption would not alter the

results of the cost-effectiveness analysis as this test was infrequently utilised (online supplemental 6). Costs of preoperative assessment were also tested in two sensitivity analyses (assuming a higher and lower cost) and results were found to be robust (online supplemental 7 and 9).

A post-operative complication rate of 4% was employed although recent data suggest this may be lower.[44,45] A lower complication rate would deem surgery more cost effective. Given the emergence of novel data since the publication of NICE Guidance in 2022 and changes in clinical practice (for example increased utilisation of sEEG), further research should refine and iteratively analyse cost-effectiveness of resective surgery. We would advocate always analysing the whole epilepsy surgical pathway across multiple centres in this future work.

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CONCLUSION

Resective epilepsy surgery is cost effective from a national health service perspective when considering all people referred for surgical assessment, not just those who proceed to resection. **Prompt referral to epilepsy surgery centres for evaluation of pharmacoresistant epilepsy would, therefore, seem essential.** Confirming cost-effectiveness of referral for epilepsy surgery should offer increased support to development and delivery of epilepsy surgery programmes.

Acknowledgements

We are grateful to all of the NICE Guideline committee and all relevant stakeholders for their input into the NICE Guideline on Epilepsies in children, young people and adults which directly led to this work.

Competing interests

The authors declare no direct conflicts of interest

Funding

This work was integral to the development of the Guideline on Epilepsies in children, young people and adults (NG217) by the National Institute for Health and Care Excellence (NICE), which is an executive non-departmental public body of the Department of Health and Social Care in England.

Contributions

The manuscript was conceptualised by AB, PK and AS with additional input throughout from SKB and DW. PK, JdT, OS, ISZ, JW, KS, VC, BZ, HF, SS, KH, LK, NM, EMA, SE, RC were involved in data collection from surgical centres. AB and DW oversaw all health economics analyses. AB, SKB, DW, PK and AS drafted and revised the manuscript with comments from all co-authors incorporated.

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Supplementary Material

Supplement 1
- Table S1: Guideline Committee members in alphabetical order of last name

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Supplement 10
- Specific populations

Supplement 11
- Table S15: Key studies evaluating cost-effectiveness of resective epilepsy surgery.

Supplement 1

Table S1: Guideline Committee members in alphabetical order of last name

Name	Role
Lauren Anderson	Lay member
Sallie Baxendale	Consultant Clinical Psychologist/Neuropsychologist
Sasha Burn	Co-optee – Consultant Paediatric Surgeon
Susan Croft	Co-optee – Emergency Medicine Physician
Helen Cross	Consultant Paediatric Neurologist and Topic Advisor
Archana Desurkar	Consultant Paediatric Neurologist
Jon Mark Dickson	General Practitioner
Sally Gomersall	Lay member
Ashley Liew	Co-optee – Consultant Neuropsychiatrist
Anna Miserocchi	Co-optee – Consultant Neurosurgeon
Lisa O'Brien	Paediatric nurse
Gareth Payne	Co-optee – Consultant Neurophysiologist
Christina Petropoulos	Paediatrician
Angie Pullen	Lay Member
Gabriella Rands	Paediatric Clinical Psychologist
Colin Reilly	Co-optee – Paediatric educational psychologist
Arjune Sen	Consultant Neurologist and Topic Advisor
Rohit Shankar	Learning disabilities psychiatrist
Philip Smith	Consultant Neurologist
Trudy Thomas	Pharmacist
Ashifa Trevedi	Co-optee – Paediatric pharmacist
Stephen Ward	Guideline Committee Chair – Consultant in Pain Medicine
Janine Winterbottom	Epilepsy Nurse Specialist

Supplement 2

Outcomes for surgery were obtained from a prospective UK study of those undergoing epilepsy surgery with a sample size of 615 people and average follow-up of 14 years .[1] Long-term outcomes for MM were obtained from an American prospective study with a sample size of 246 and a follow-up of five-years.[2]

The number of people relapsing and entering remission after surgery is presented graphically by de Tisi and colleagues.[1] This graphic provided a breakdown of the number of people in four distinct categories that are presented in Table S2.

Table S2: Categorisation of post-operative state [1]

	Category
Category One	Seizure free this year and not seizure free the subsequent year
Category Two	Seizure free this year and seizure free the subsequent year
Category Three	Not seizure free this year and seizure free next year
Category Four	Not seizure free this year and not seizure free the subsequent year

Data for the number of people in each category were provided up to and including year 15, although the number of people lost to follow-up increased annually. Data were extracted from the graph using DigitizeIt® to determine the total number of people residing in each category (Table S3).[3]

The probability of relapse (transitioning from 'seizure free' to 'not seizure free') was calculated by first subtracting the number of people seizure free this year and the subsequent year from the number of people seizure free this year and not seizure free in the subsequent year (Category One – Category Two). The result was then divided by the number of people who were seizure free this year and not seizure free the subsequent year (Category One). The number of people residing in each category and the corresponding probabilities for each year up to year 15 are presented in Table S3.

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

Table S3: The probability of relapse for surgery

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%
14	15	51	46	8.3%
15 – 84	16 - 85	-	-	4.2%

The probability of remission (transitioning from ‘not seizure free’ to ‘seizure free’) was calculated as detailed above but this time for people initially in the ‘not seizure free’ categories ([Category Three – Category Four] / Category Three). The resulting probabilities for remission up to year 15 are presented in Table S4.

Given data were only available up to year 15 – data for the remaining lifetime horizon of the model needed to be extrapolated. Beyond year ten there was no clear trend in the data, so a constant hazard was estimated using the data from year 11 to year 15, resulting in an annual probability of 7.6%.

The NICE Guideline Committee (GC) 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). Calculating the probability of remission using data from year six to year 15, as was done for the probability of relapse, resulted in a probability of remission of 9.7%. The GC concluded that a probability of 9.7% for remission from year 16 onwards would very likely be overestimating the probability of remission.

Table S4: The probability of remission for surgery

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	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%
15 - 84	16 - 85	-	-	7.6%

A beta distribution was applied to the calculated probabilities presented in Table S3 and Table S4 for the probabilistic analysis.

In most long-term outcome studies assessing the effectiveness of epilepsy surgery, seizure freedom was defined as being completely seizure free or with only focal aware seizures (seizures in which there is no loss of contact with environs).[1] Whilst clinically appropriate, as focal aware seizures are associated with less risk and impairment than focal to bilateral tonic clonic (convulsive) seizures, this definition did not correspond with that used in the RCTs. Studies exploring health state utilities and SMRs, only evaluated people who were completely seizure-free. To overcome the challenges posed by these differential definitions, adjustments were made to the SMRs (Supplement 3) and utilities (Supplement 4) for seizure freedom in the surgery arm using the proportion of people that experienced focal-aware seizures listed previously.[1] The utility and mortality for people experiencing only focal aware seizures is not known, and so conservative assumptions were made, which, if anything, might have under-estimated the benefits of surgery. As only 18% of people of the seizure free sample had experienced focal aware seizures following surgery, the committee concluded this would not alter the overall results of the cost-effectiveness analysis.

The long-term MM study defined drug resistant epilepsy as people who had failed at least two ASMs and were experiencing at least one seizure per month.[2] This is stricter than the current International League Against Epilepsy (ILAE) definition of drug resistant epilepsy being the occurrence of uncontrolled seizures despite two tolerated and appropriately chosen ASMs. Therefore, the cohort of people in the MM study we utilised may have had more severe drug refectory epilepsy compared to a drug resistant cohort as defined by the ILAE.[2] The committee did however note that the estimated proportion of people entering seizure freedom (5.6%) and relapsing (22%) each year seemed compatible with what is observed in clinical practice

Supplement 3

The Standardised Mortality Ratio (SMR) for being 'seizure free' in the surgery arm was adjusted due to different definitions of seizure freedom in our two long-term outcomes studies. Callaghan and colleagues defined seizure freedom as completely seizure free,[2] whereas de Tisi and colleagues defined seizure freedom as either completely seizure free or seizure free except for 'simple partial seizures' (now termed focal aware seizures, FAS).[1] It was calculated from the work of de Tisi and colleagues that 82% of people at the end of follow-up were completely seizure free.[1] Therefore, the SMR for seizure free in the surgical arm was calculated by multiplying this proportion (82%) by the SMR for people who are seizure free (1.78) and adding this value to the proportion of those not completely seizure free (18%) multiplied by the SMR for not seizure free (5.40).

Of note, the SMR for 'seizure free' used in the base case analysis was obtained from one of the two studies used in the pooled SMR (1.11) reported by Choi and colleagues.[4] The SMR reported by Salanova and colleagues was used in the base case analysis,[5] and the pooled SMR was discarded for the base case, because Sperling and colleagues reported zero deaths, which the GC thought was likely unfeasible to apply in modelling.[6]

Supplement 4

Utility values used in the model were obtained from Väätäinen and colleagues.[7] The health state utility values reported by Väätäinen and colleagues, however, were for; seizure free, ≥50% reduction in seizures, and <50% reduction in seizures and therefore did not align to the health states in our model ('seizure free' and 'not seizure free').[7]

The utility value for seizure free reported by Väätäinen and colleagues was used for the health state utility value for seizure free in the Medical Management (MM) arm.[7] Owing to the differing definitions of seizure freedom in our two long-term outcome studies (as outlined in Supplement Three),[1,2] the utility value for seizure free in the surgery arm was calculated to account for the differing definitions of seizure freedom (see Supplement Three and Table S5).

To estimate the utility value of 'not seizure free', data from Neligan and colleagues were used.[8] Neligan and colleagues provided data on the number of people in a drug refractory cohort of 139 people receiving medical management in the UK who achieved seizure freedom, a 50% to 99% improvement in seizures or <50% improvement in seizures.[8] Thus, allowing us to assign a proportion to the utility values reported in Väätäinen and colleagues to calculate a value of 'not seizure free'.[7]

Neligan and colleagues reported that at the end of follow-up, 29.50% (41/139) of people experienced a 50%-99% reduction in seizures and 51.80% (72/139) of people experienced a <50% reduction in seizures.[8] Subsequently, to calculate the utility value of 'not seizure free' in our model, the absolute proportion of people who had experienced a ≥50% reduction in seizures and <50% reduction in seizures were calculated. Overall, 36.28% of people experienced a ≥50% reduction in seizures (29.50% / [29.50%+51.80%]) and 63.72% (100 – 36.28%) experienced a <50% reduction in seizures.[8] These proportions where then multiplied to the corresponding utility values reported by Väätäinen and colleagues to obtain a utility value for not being seizure free (Table S5).[7]

Table S5: Utility data inputs and values used in the model

Health state	Utility value	Source
Full health	1.000	By definition
Seizure free MM	0.869	Väätäinen and colleagues[7]
≥50% reduction in seizures	0.805	Väätäinen and colleagues[7]
<50% reduction in seizures	0.623	Väätäinen and colleagues[7]
Not seizure free	0.689	=0.805x36%+0.623*64%
Seizure free surgery	0.858	=0.869x82%+0.805*18%

To make utility values probabilistic, utility decrements between states were calculated from the data reported in Väätäinen and colleagues.[7] Utility decrements reported in Table S6 are calculated based on values reported in Table S5.

Table S6: Utility decrements

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

Probabilistic values were calculated for the utility decrements (Table S6) using a gamma distribution. The resulting probabilistic values for the utility values reported in Väätäinen and colleagues were calculated in the following way:[7]

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

The method outlined above keeps the utility rank the same.

Supplement 5

Data capture form completed by participating UK surgical centres for a minimum of 50 consecutive patients evaluated by their epilepsy surgery programme.

Pre-Surgical Evaluation Tests																
History & Examination	Neuropsychology assessment	Neuropsychiatry assessment	MRI	Initial video telemetry	Repeat video telemetry	PET	Occupational therapy	Physiotherapy	sEEG	SPECT	fMRI	Amytal testing	MEG	Multidisciplinary team meeting	Pre-surgical counselling	Informed consent assessment	Other (please give details)

	Outcome of evaluation					
Total number of patients referred for pre-surgical evaluation	Number of patients not eligible for surgery	Number of patients eligible for surgery but did not consent to surgery	Number of patients eligible for surgery and surgery went ahead	Number of patients eligible for surgery and surgery is due to take place (with the type of surgery known)	Number of patients eligible for surgery and surgery is due to take place (with the type of surgery unknown)	Other (please give details)

	Type of Surgery												
Total number of patients referred for pre-surgical evaluation	Hemispheric disconnection	Total lobectomy of brain	Partial lobectomy of brain	Excision of tissue of frontal lobe of brain	Excision of tissue of temporal lobe of brain	Excision of tissue of parietal lobe of brain	Excision of tissue of occipital lobe of brain	Complete callosotomy	Partial callosotomy	Hypothalamic hamartoma resection	Disconnective surgery	Other	**Total**

Supplement 6

Table S7: Cost of pre-surgical assessment

Test	Mean number of tests per person (n=762)	Unit cost	Mean cost per patient investigated	Probability distribution	Source
History & Examination	1.4	£225	£315	Gamma (Alpha: 25, Beta: 0.1)	**NHS reference costs using** currency codes WF01B and WF01A – assuming everyone has one initial appointment and 40% of people have a second appointment
Neuropsychology assessment	0.9	£334	£291	Beta (Alpha: 664, Beta: 98)	**NHS reference costs** Currency code: AA32Z: Neuropsychology tests, outpatient procedures
Neuropsychiatry assessment	0.5	£346	£157	Beta (Alpha: 345, Beta: 417)	**NHS reference costs** Currency code: WF01B: Consultant led, non-admitted face-to-face attendance, first, service code 656, Clinical psychology
Magnetic resonance imaging (MRI)	1.6	£146	£234	Gamma (Alpha: 25, Beta: 0.1)	**NHS reference costs** Currency code: IMAGOP: Imaging: Outpatient, currency code: RD01A Magnetic Resonance Imaging scan of one area, without contrast, 19 years and over
Initial videotelemetry	0.9	£2,791	£2,630	Beta (Alpha: 718, Beta: 44)	**NHS reference costs** Currency code: AA80Z Elective complex long-term EEG monitoring
Repeat videotelemetry	0.3	£2,791	£736	Beta (Alpha: 201, Beta: 561)	**NHS reference costs** Currency code: AA80Z Elective complex long-term EEG monitoring
Positron emission tomography (PET)	0.4	£666	£270	Beta (Alpha: 309, Beta: 453)	**NHS reference costs** Currency code: AA80Z Elective complex long-term EEG monitoring
Occupational therapy	0.0052	£111	£0.58	Beta	**NHS reference costs**

				(Alpha: 4, Beta: 758)	Currency code: WF01B Consultant led, non-admitted face-to-face attendance, first, service code 651, Occupational Therapy
Physiotherapy	0.0052	£59	£0.31	Beta (Alpha: 4, Beta: 758)	**NHS reference costs** Currency code: WF01B Consultant led, non-admitted face-to-face attendance, first, service code 650, Physiotherapy
Stereo electro-encephalography (sEEG)	0.2	£14,638	£2,497	Beta (Alpha: 130, Beta: 632)	**NHS reference costs** Currency code AA83Z Elective intracranial telemetry
Single-photon emission computed tomography (SPECT)	0.1	£342	£31	Beta (Alpha: 68, Beta: 694)	**NHS reference costs** Currency code: IMAGOP: Imaging: Outpatient, Currency code RN04A single photon emission computed tomography with computed tomography (SPECT-CT) of one area, 19 years and over
Functional magnetic resonance imaging (fMRI)	0.4	£146	£55	Beta (Alpha: 288, Beta: 474)	At the time of model development, the Guideline Committee (GC) took the assumption that fMRI and MRI costs would be the same as no NHS fMRI costing were available. The GC also surveyed advice from centres where fMRI was performed.
Amytal testing	0.0354	£3,545	£126	Beta (Alpha: 27, Beta: 735)	Cost obtained from participating surgical centres
Magnetoencephalography (MEG)	0.0197	£3,250	£64	Beta (Alpha: 15, Beta: 747)	Cost estimated from participating surgical centres (between £2,000 and £4,500)
Multidisciplinary team meeting (MDT)	1.6	£229	£362	Gamma (Alpha: 25, Beta: 0.1)	**NHS reference costs** Currency codes WF02B and WF02A assuming everyone receives an

					initial MDT and 60% of people receive a second
Pre-surgical counselling	0.7	£346	£235	Beta (Alpha: 517, Beta: 245)	NHS reference costs Currency code: WF01B: Consultant-led, non-admitted face-to-face attendance, first, service code 656, Clinical psychology
Informed consent assessment	0.4	£224	£83	Beta (Alpha: 284, Beta: 478)	**NHS reference costs** Currency code: WF01B, Consultant led, non-admitted face-to-face attendance, first, service code 150, Neurosurgery
Electrocorticography (ECoG)	0.0236	£4,000	£94	Beta (Alpha: 59, Beta: 2)	Cost estimated from participating surgical centres (between £3,000 and £5,000)
Total cost					£8,181.52

Source of costs NHS reference costs 2019/20 unless stated otherwise.[9]

All costs presented were obtained from NHS reference costs contemporaneous with development of NICE Guideline 217. **NHS reference costs are the average unit costs of providing various healthcare services within the NHS in England. Within England, these costs are used to set prices for NHS-funded services, understand NHS expenditure, and compare performance between different NHS organizations. NHS reference costs are commonly used within NICE guidelines as these likely capture the most accurate cost incurred for the NHS. These costs are, however, presented to guideline committee members for validation as occasionally NHS reference costs can over or under inflate costs due to either, data categorisation, or a low reported number of events and given costs for a specific intervention.**

Different centres performed certain investigations to varying degrees. For example, certain centres would routinely perform fMRI and MEG recordings, whereas other centres did not have access to such testing.

The cost of fMRI was assumed to be the same as MRI due to a lack of data. Although the guideline committee acknowledged the cost may be greater in clinical practice, they noted that resource use for this test was relatively low and therefore the sensitivity analysis assuming a higher cost for pre-surgical evaluation would overcome this limitation (Tables S11 and S13). Most importantly, though, there is now much greater utilisation of stereo-EEG across all centres. The costs per stereo-EEG recording are also escalating – for example deployment of a greater number of electrodes, more time in planning electrode mapping and potentially longer recordings. Sensitivity analyses for stereo EEG were performed (Table S11 and Table S13). However, in the future it would seem important to perform specific subgroup analysis of people undergoing stereo-EEG implantation to determine the cost-effectiveness of such procedures now that costs and utilisation are higher.

The cost of resective epilepsy surgery was based on the average of all relevant surgical currency codes for adult resective surgery, weighted according to the total number of Finished Consultant Episodes (FCE's) for each code. The weighted average total cost of surgery used in the health economic model was £10,185. The costs of each currency code and number of FCEs as well as the weighted average total cost of surgery are presented in Table S8.

The cost of resective epilepsy surgery was made probabilistic by applying a gamma distribution (Mean = 10,185; SE = 20% of mean).

Table S8: Cost of resective epilepsy 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
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	£10,332
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
Weighted average cost			£10,185

Source: NHS reference costs 2019/20.[9]

For a brief description of NHS reference costs please see the text below Table S7 in supplement 6.

Table S9: 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]	£42	£15.12
	Not seizure free	61%[d]		£51.24

Sources:

(a) NHS reference costs 2019/20.[9]

(b) PSSRU 2022, GP consultation (9.22 minutes), including qualification costs and direct care costs NHS reference costs 2019/20[9]

(c) Assumption based on GC opinion

(d) Jacoby and colleagues[10]

Costs of outpatient contacts were dependent on whether, and for how long, someone was seizure free. For example, initial follow-up costs were higher in the surgery arm owing to post-operative follow-up.

PSSRU unit costs are a comprehensive collection of cost estimates for various health and social care services, representing the cost incurred to the NHS. For a brief description of NHS reference costs please see the text below Table S7 in supplement 6.

Table S10: Cost of admissions

	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:

(a) Annual probability of accessing a service if seizure free, from Jacoby and colleagues[10]
(b) Committee opinion from previous NICE guideline (CG137)[11]
(c) GC opinion
(d) NHS reference costs 2019/20[9], Inpatient admission (Currency code AA26F), A&E admission (Currency code VB08Z)

For a brief description of NHS reference costs please see the text below Table S7 in supplement 6.

Table S11: Cost of Anti-seizure medications

Drug	**Preparation**	**Mg/day**	**Cost per year (£)**	**Weighting[(a)]**	**Total cost**
Brivaracetam	Tablet	150	£1,267	3.9%	£49.85
Carbamazepine	Modified-release tablets + tablets	1400	£174	20.0%	£34.81
Clobazam	Tablet	30	£236	3.9%	£9.27
Eslicarbazepine	Tablet	1200	£1,214	3.9%	£48.81
Gabapentin	Capsule	3150	£108	0.3%	£0.36
Lacosamide	Tablet	350	£1,785	3.9%	£70.22
Lamotrigine	Tablet	500	£43	20.0%	£8.54
Levetiracetam	Tablet	3000	£104	20.0%	£20.81
Oxcarbazepine	Tablet	2100	£989	3.9%	£38.90
Perampanel	Tablet	6	£1,825	3.9%	£71.78
Pregabalin	Capsule	500	£78	0.3%	£0.26
Phenytoin	Capsule	400	£252	3.9%	£9.91
Sodium valproate	Modified-release tablets + tablets	2000	£357	3.9%	£14.06
Topiramate	Tablet	450	£395	3.9%	£15.53
Zonisamide	Capsule	450	£1,006	3.9%	£39.58
Total average cost for one ASM					£432.70

Source: British National Formulary (BNF)[12] **– costs from the BNF represent the cost of a drug to the NHS**.

(a) GC opinion

The total cost of ASMs was calculated to be £1,082 – assuming people receive on average 2.5ASMs.
Of note, the following costs were updated to current values and so differ slightly from those in the published NICE guidance:[13]

- History & Examination – pre-surgical evaluation cost;
- Multidisciplinary team meeting (MDT) – pre-surgical evaluation cost;
- GP consultation cost;
- Anti-seizure medication costs

Supplement 7

Table S12: List and description of one-way sensitivity analysis

One-way sensitivity analysis	Description of sensitivity analysis
Utilities assuming 50% of people in the surgery arm have a ≥50% reduction in seizures	In the base case analysis, utility values for not seizure free were calculated weighting the proportion of people who achieved a ≥50% reduction in seizures and a <50% reduction in seizures based on data reported in Neligan and colleagues.[8] However, because the study population in Neligan and colleagues was for a drug refractory cohort of people 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.[8] This increased the utility value for 'not seizure free' surgery from the base case value of 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 as follows: 'Seizure free' medical management – 0.869 'Seizure free' surgery – 0.858 'Not seizure free' medical management – 0.689 'Not seizure free' surgery – 0.714 (i.e., the utility value for 'Not seizure free' surgery changes from 0.689 to 0.714)
Utilities from Kovacs and colleagues[14]	Using the method outlined in Supplement Four, utility values from Kovacs and colleagues were used in one-way sensitivity analysis.[14] The resulting utilities were: Seizure free medical management – 0.894 Seizure free surgery – 0.831 Not seizure free– 0.543
Utilities from the previous NICE guideline	The utility values reported in the study used to calculate the utility values in the base case were 0.869, 0.805, and 0.623 for seizure free, a ≥50% reduction in seizures, and <50% reduction in seizures respectively.[7] The utility values used in the previous NICE guideline (GC137) model assessing the cost effectiveness of different ASMs for monotherapy and add-on therapy,[11] had a smaller utility difference compared to those reported in Väätäinen and colleagues.[7] 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 and colleagues.[7] It is not clear why the utility values from the previous NICE guideline model are quite different but the ones from Väätäinen and colleagues 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.[7] The values in the previous model also seemed implausibly high, being above the general population mean on average. The utilities from the previous NICE guideline model were used in a one-way sensitivity analysis. The same methods outlined in Supplement Four were used to calculate the utility values used in the health economic model. The utility values used in the model for this sensitivity analysis were: Seizure free medical management – 0.940 Seizure free surgery – 0.933 Not seizure free – 0.862
The probability of receiving surgery is higher	Out of the ten epilepsy surgery centres who submitted data as part of the assessment for resective epilepsy surgery survey, at two centres the calculated probability of being a surgical candidate was 60%. This value of 60% was the highest probability out of all the participating centres and therefore used in the sensitivity analysis.
The probability of receiving surgery is lower	The lowest probability of being a resective epilepsy surgery candidate of the individual ten participating centres was 26%.
Treatment effects from Wiebe 2001 only[15]	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.[16,17] However, a sensitivity analysis was conducted using the treatment effects from Wiebe and colleagues only.[16] This is because the study by Engel and colleagues was a smaller RCT owing to the fact that the trial was terminated early as a result of poor recruitment.[17] The probability of 'not being seizure free' using data from Wiebe and colleagues was calculated as the total number of events divided by the total number of people (37/39) resulting in a probability of 94.9%.[16] The probability of 'not being seizure free' for the surgery arm was calculated by multiplying the risk ratio (0.45) by the probability of not being seizure free for medical management (94.9%). Using data from Wiebe only resulted in a higher probability of 'not being seizure free' after epilepsy surgery (42.71% compared to 40.6% in the base case).

SMR for seizure free is 1.11	The SMR for 'seizure free' used in the base case analysis was obtained from one of the two studies used in the pooled SMR (1.11) reported by Choi and colleagues.[4] The SMR reported by Salanova and colleagues was used in the base case analysis,[5] and the pooled SMR was discarded for the base case, because Sperling and colleagues reported zero deaths, which the GC thought was likely unfeasible.[6] A sensitivity analysis was therefore conducted using the pooled SMR from Choi and colleagues to assess the impact on the results.[4]
Surgery relapse rate higher	A scenario analysis was conducted assuming the relapse rate in the surgery arm was 20% higher.
Surgery relapse rate lower	A scenario analysis was conducted assuming the relapse rate in the surgery was 20% lower.
Pre-surgical evaluation costs higher	The highest total assessment cost across the ten centres was used: £13,178.
Pre-surgical evaluation costs lower	The lowest total assessment cost across the ten centres was used: £5,474.
Surgery cost 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.
Surgery cost lower	A sensitivity analysis was conducted assuming a lower 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.
Time horizon 15 years	RCT data were only available for up to 2 years.[15,17] In addition, the data to inform the long-term outcomes were 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 to eliminate the extrapolation of data in the surgery arm. This sensitivity analysis span the duration of the surgery arm data., but MM extrapolation was still employed in this analysis (10 years).
No discontinuation of ASMs	In the base case analysis, discontinuation of ASMs was assumed to be for 15.7% for people who were seizure free for 3 or more years. A sensitivity analysis was conducted assuming no discontinuation of ASMs because of the uncertainty surrounding the number of people who choose to come off ASMs.

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 GC 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.[9] 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 standard sEEG implantation and 40% of people received more complex sEEG implantation. For the cost of standard sEEG we used the NHS reference cost (£14,638) and for the more complex sEEGs we averaged the 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.
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 being 1.11 • a higher proportion of people were eligible surgery candidates (60%), • the utility values from Kovacs and colleagues.[14]
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 • a time horizon of 15 years • utility values from the previous guideline model Of note, the higher cost for SEEG was not included in the higher average cost of assessment for resective epilepsy surgery as these two analyses were run separately.

Supplement 8

List of participating United Kingdom surgical centres:

- Complex Epilepsy and Surgery Service, Neurosciences Centre, Queen Elizabeth Hospital Birmingham.
- Bristol Adult Epilepsy Surgery Programme, Southmead Hospital, North Bristol NHS Trust, Bristol.
- Epilepsy Surgical Service, Cardiff University Hospitals, Cardiff.
- Epilepsy Surgery Service, Kings College Hospital, London.
- The Walton Centre NHS Foundation Trust, Liverpool.
- Surgical Centre – Manchester Centre for Clinical Neurosciences, Salford Royal, Northern Care Alliance NHS Foundation Trust, Manchester.
- The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne.
- Oxford Comprehensive Epilepsy Centre, John Radcliffe Hospital, Oxford.
- Wessex Neurological Centre, University Hospital Southampton NHS Foundation Trust, Southampton.
- NIHR University College London Hospitals Biomedical Research Centre, UCL Queen Square Institute of Neurology, London.

Supplement 9

Table S13: Deterministic results

	Surgery	**Medical management**	**Surgery minus medical management**
Assessment for resective surgery	£19,809	£0	£19,809
Surgery	£10,185	£0	£10,185
Appointment costs	£3,623	£5,513	-£1,890
Anti-seizure medication costs	£14,506	£20,017	-£5,510
Admissions	£3,242	£6,943	-£3,701
Reoperations	£663	£0	£663
Complications	£3,797	£0	£3,797
Total cost	£55,825	£32,473	£23,352
Mean QALYs	15.89	13.75	2.14
Incremental cost per QALY gained			£10,932

Results of the one-way sensitivity analyses can be found in Table S14. A full description of the analyses can be found in Supplement 7.

Table S14: One-way sensitivity analysis results (deterministic)

Scenario	Incremental costs	Incremental QALYs	Incremental cost per QALY gained
Determinist base case	£23,352	2.14	£10,932
Probabilistic base case	£24,422	2.15	£11,348
Utilities assuming 50% of people in the surgery arm have a ≥50% reduction in seizures	£23,352	2.30	£10,150
Utilities from Kovacs and colleagues[14]	£23,352	3.04	£7,686
Utilities from the previous NICE guidance	£23,352	1.33	£17,587
The probability of receiving surgery is higher	£17,179	2.14	£8,042
The probability of receiving surgery is lower	£35,010	2.14	£16,389
Treatment effect from Wiebe and colleagues only[16]	£23,485	2.10	£11,175
SMR for seizure free is 1.11	£23,477	2.34	£10,037
Surgery relapse rate higher	£24,380	1.96	£12,470
Surgery relapse rate lower	£22,190	2.34	£9,491
Assessment for resective surgery costs higher	£35,629	2.14	£16,679
Assessment for resective surgery costs lower	£16,699	2.14	£7,817
Surgery costs higher	£29,534	2.14	£13,826
Surgery costs lower	£21,477	2.14	£10,054
Time horizon 15 years	£26,869	0.96	£28,093
No discontinuation of anti-seizure medications	£29,852	2.14	£13,974
Higher cost for sEEG	£27,534	2.14	£12,889
Overall best case	£9,651	3.54	£2,728
Overall worst case	£66,703	0.37	£181,764

Supplement 10

Epilepsy disproportionately affects people from lower socio-economic groups. Despite this, even in high-income countries, the number of people from poorer backgrounds referred for specialist care is lower than from richer deciles resulting in both diagnostic and treatment gaps.[18] In low to middle income countries (LMICs) such gaps are much larger, the risks from seizures greater (for example owing to cooking on open fires; washing clothes in rivers – situations in which seizures are much more likely to result in harm) and stigmatisation of epilepsy can be very marked.[19] Inconsistency in the supply of medication also associates with specific hazard. 'Stock outs' may mean that people are suddenly without ASMs for several months resulting in worse and more frequent seizures for those with drug refractory epilepsy as well as associated morbidity and mortality.

Epilepsy surgery, it could be argued, is therefore more needed in LMICs as it offers the possibility of seizure remission and, potentially, less need for ASMs.[20] Although there are limited data on epilepsy surgery in LMICs, favourable outcomes are reported.[21–24] Certain centres in LMICs are also able to offer work up of complex cases, including intracranial recording, again demonstrating positive outcomes,[21,25] whilst others have developed models of data sharing to enable consensus treatment decisions.[22,26]

Relatively few data are available on the costs of resective epilepsy surgery in LMICs. In Panama, for example, the cost was estimated at USD 9,850 per patient although this included intraoperative corticography as well as invasive intracranial recording.[26] An Indian team identified appropriate surgical candidates using the minimal required tests of video-EEG and 1.5 Tesla MRI scans and estimated a total cost (investigations and the operation itself) of Rs 92707 (USD 1,324).[27] In this cohort Engel Class 1A outcomes (completely free of seizures following epilepsy surgery) were observed in 92.5% of people with more than one year of follow up.[27]

Overall, costs for epilepsy surgery are substantially less than in high-income settings with potentially greater benefits.[28] Although costs are lower in LMICs, these countries will typically have a smaller budget for health care and therefore cost-effectiveness thresholds will be lower. Our model illustrated that resective epilepsy surgery is highly cost-effective providing a clear mandate that appropriate individuals are considered for resective epilepsy surgery in LMICs.

Supplement 11

Table S15: Key studies evaluating cost-effectiveness of resective epilepsy surgery.

Publication	Intervention and Population	Method	Cost Effectiveness Result
Kovacs and colleagues[14]	Intervention 1: Stereo electroencephalography (SEEG) followed by resective surgery (if appropriate) in patients with drug-resistant, focal-onset epilepsy versus medical management. Intervention 2: Placement of subdural grid electrodes (SDGs) followed by resective surgery (if appropriate) in patients with drug-resistant, focal -onset epilepsy versus medical management. Hungarian payer perspective.	Decision analytic model consisting of a 1-year decision tree and 30-year Markov model. Cohort starting age 35. Assumed 100% compliance to interventions and surgery. Analysis did not include other preoperative assessment costs. One-way sensitivity analyses and probabilistic sensitivity analysis. The incremental cost-effectiveness ratio (ICER) was set at three times the GDP per capita regarding the previous year (€41,058). QALYs used to determine is surgery is cost-effective.	ICER of SEEG is €4607 per QALY gained. ICER of SDG is €3013 per QALY gained. As SEEG and SDG were found to be cost-effective – this infers that resective epilepsy surgery is also cost-effective.

Sheikh and colleagues[29]	Drug resistant temporal lobe epilepsy surgery versus medical management. USA single centre study.	Excluded intracranial EEG cost. Lifetime time horizon. Semi-Markov decision-analytic model. One-way sensitivity analyses and probabilistic sensitivity analysis. The incremental cost-effectiveness ratio (ICER) to societal willingness to pay (approximately $100,000 per quality-adjusted life-year. (QALY) was used to determine whether surgery is cost-effective.	Epilepsy surgery is cost-effective compared to medical management in surgically eligible patients by virtue of being cost-saving ($328,000 vs $423,000) and more effective (16.6 vs 13.6 QALY) than medical management in the long term.
Kitwitee and colleagues[30]	Video-Electroencephalography monitoring followed by surgery or medical management versus no video-electroencephalography (and medical management). Thailand; single centre.	Hypothetical cohort. 40-year time horizon. Markov model. One-way sensitivity analyses, threshold analysis, and probabilistic sensitivity analysis.	Cost-effective form both societal and health care perspectives.
Picot and colleagues[31]	Epilepsy surgery for people with drug resistant focal epilepsy versus medical management. Nationwide French study.	Excluded patient who underwent evaluation and deemed inoperable. Prospective data collection. Lifetime time horizon. Monte-Carlo simulation based on the Markov transitional model.	Impact per QALY not stated. Cost-effectiveness in the medium term. At 2 years, the mean direct medical cost per patient and per year was 2,990 € in surgery group and 3,550 €

		One-way sensitivity analyses and multivariate sensitivity analysis.	in medical group, resulting in an ICER of around 10,500 € per seizure-free patient. The value of the discounted ICER was 10,406 (95% confidence interval [CI] 10,182–10,634) at 2 years and 2,630 (CI 95% 2,549–2,713) at 5 years.
Burch and colleagues[32]	Intervention 1: Medical management (MM) Intervention 2: Fluorodeoxyglucose positron emission tomography (FDG-PET) - If positive, people offered surgery. - If negative, people offered MM. - If uncertain, people offered MM. Intervention 3: FDG-PET - If positive, people offered surgery. - If negative, people offered MM. - If uncertain, people offered Electroencephalography (iEGG).	Decision analytic model consisting of a 1-year decision tree that captures the tests and 1-year outcomes following the interventions (surgery or medical management). Includes complications (transient or permanent) and quality of life impact. At the end of the short-term model, people could either: be having disabling seizures; have achieved seizure freedom; or have died. The Markov model had an additional 3 tunnel states to track how long people were seizure fee (SF; SF for 1 year, SF for 2 years, SF for > 2 years (on or off antiseizure medications). Starting age of cohort 35.	ICER of Intervention 2 versus Intervention 1: - £1671 per QALY gained Probability Intervention 2 cost effective (£20K/30K threshold): 3%/3%. ICER of Intervention 3 versus Intervention 2 - £3201 per QALY gained Probability Intervention 3 cost effective (£20K/30K threshold): 83%/84%. As interventions were found to be cost-effective this infers that surgery is also a cost-effective strategy.

		Lifetime horizon. One-way sensitivity analyses and probabilistic sensitivity analysis. The incremental cost-effectiveness ratio (ICER) was £20,000 per QALY gained.	
Platt and Sperling[33]	Epilepsy surgery for people with drug resistant temporal lobe epilepsy versus medical management. USA single centre study.	Group level analysis based upon outcome of seizure frequency at follow up. Mortality not taken into account in a 40-year model. Cost comparison study Evaluation did not consider QALYs or ICER.	Depending on which costs are included in the analysis, a surgical management approach could be shown to become more cost-effective in as little as 7.3 years, or as much as 35 years.
Langfitt[34]	Drug resistant temporal lobe epilepsy surgery versus medical management. Multiple USA centre study.	Intervention considered cost effective if marginal cost effectiveness ratio > $50,000/QALY. Decision analysis model. One-way sensitivity analyses, and multiway sensitivity analysis. Limitation of small sample size owing to lack of patient records available in recruited patients (58.7% of recruited).	Base case analysis yielded a marginal cost effectiveness ratio (MECR) of US $15,58 quality-adjusted life year (QALY).

King and colleagues[35]	Drug resistant temporal lobe epilepsy surgery versus medical management. USA single centre study.	Included patients undergoing. intracranial EEG, and those who did not proceed to surgery. Lifetime time horizon. One-way sensitivity analyses. Markov state transitional model.	Combining the clinical and economic outcomes yielded a cost-effectiveness ratio of $27,200 per QALY. The cost per QALY of evaluation for ATL is comparable to other widely practiced medical and surgical interventions.
Wiebe and colleagues[15]	Drug resistant temporal lobe epilepsy surgery versus medical management. Analysis based on a Canadian single centre study.	Costs partly based upon 30 patients from single centre. Indirect costs not included. 35-year time horizon. One-way and two-way sensitivity analyses. Decision tree model. Evaluation did not consider QALYs or ICER.	Cost time curves intersected at 8.5 years and became cheaper for surgical patients thereafter compared to medical managed group.

Sánchez Fernádez and colleagues[36]	Comparison of total healthcare cost before and after epilepsy surgery. . Privately insured adults and children in the USA.	Retrospective descriptive study of costs of outpatient visits, emergency department visits and hospital admissions five years before and after surgery. Data obtained from a commercial healthcare database The study did not include indirect societal or medication costs.	Temporal, extratemporal and hemispherectomy surgery had lower direct healthcare costs related to hospital-based care over five years. Epilepsy surgery resulted in cost of $7691 cost per person per year compared to $18750 per person per year prior to surgery ($p<0.0001$)). Corpus callosectomy did not reduce costs over five years.

Detailed systematic review of the cost effectiveness of all epilepsy surgery interventions can be found elsewhere.[37–39]

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