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Cost-effectiveness of epileptic surgery compared with medical treatment in children with drug-resistant epilepsy

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ABSTRACT

Background: Epilepsy surgery is an alternative to continued antiepileptic drugs (AEDs) in children with drug-resistant epilepsy (DRE).
Objective: The objective of the study was to measure, model, and compare the medical costs and impacts on health-related quality of life (HRQL) of epilepsy surgery versus continued medical treatment with AEDs in children with DRE.
Methods: A decision analytic model was created to estimate the cost-effectiveness of epilepsy surgery relative to continued medical treatment with AEDs. The model was based on costing and effectiveness data collected from 105 children with DRE who were operated on at the Royal Children's Hospital, Melbourne, Australia. The mean cost of conducting epilepsy surgery was AU$ 61,417 per person. Effectiveness of continued medical treatment was sourced from best available literature. In the absence of published utility values for pediatric patients with epilepsy and ethical approval to contact patients directly, HRQL was estimated by four clinicians using the Child Health Utility 9 Dimension (CHU9D). Outcome measures were seizure freedom and quality-adjusted life years (QALYs).
Results: The costs over 7.6 years of follow-up were AU$ 219,297 for the surgical treatment group compared with AU$ 170,583 for the medical treatment group. The incremental cost-effectiveness ratio (ICER) for surgically vs medical treatment was AU$ 76,538 per additional patient attaining seizure freedom and AU$ 75,541 per additional QALY gained.
Conclusion: Epilepsy surgery resulted in a greater reduction of seizures and improvement in HRQL but was more expensive than continued medical treatment with AEDs. Including benefits outside of a healthcare perspective would likely lead to a more compelling cost-effective argument.

1. Introduction

Patients with epilepsy incur high direct healthcare expenditure because of diagnostic investigations, medical treatment, and hospitalization [1]. The national impact of epilepsy in the United States, in terms of medical expenditures and informal care, was estimated at US$ 10 billion dollars in 2004 [1]. Indirect costs such as missed educational opportunities and underemployment or unemployment can also be significant [2].

Up to 70% of patients with epilepsy achieve seizure remission [3] with antiepileptic drugs (AEDs) [4,5]. It is estimated that 14% of treated patients will require second-line or third-line AEDs to achieve seizure control [6–8]. However, at least 20% of adults [6] and 10% of children with newly diagnosed epilepsy develop drug-resistant epilepsy (DRE) [9].

Annual healthcare costs in children with uncontrolled epilepsy are significantly higher than those with stable epilepsy. In 2014, the costs for patients with uncontrolled epilepsy and patients with stable epilepsy were calculated at US$ 30,343 vs US$ 18,206 [10].

Epilepsy surgery is an alternative to continued AEDs in children with DRE, with potential for improved neurodevelopmental outcome and family functioning [11]. Various studies report improvements in health-related quality of life (HRQL) in children undergoing epilepsy surgery [12–16]. Most of the economic research on epilepsy surgery is in adults and suggests substantial cost-savings compared

Abbreviations: HRQL, health-related quality of life; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; CHU9D, Child Health Utility 9 Dimension; PSA, probabilistic sensitivity analysis.

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with medical treatment [17,18]. There is little economic research on epilepsy surgery in children and none that incorporates longer term impacts including HRQL.

An economic evaluation provides health systems and decision makers with population level evidence on whether an intervention represents value for money. An economic evaluation incorporates both the costs involved in providing the healthcare intervention and the changes in costs arising because of the intervention. The costs are then evaluated in terms of the effectiveness of the intervention. Effectiveness may be measured in two ways: the clinical outcome of the intervention, for example, seizure freedom or in quality-adjusted life years (QALYs). Quality-adjusted life years express the benefits of healthcare treatment and preventative programs in a common metric that facilitates comparison across diseases and conditions. Quality-adjusted life years are calculated based on patient-rated questionnaires of HRQL. The cost and effectiveness of the intervention are then summarized into a single measure known as an incremental cost-effectiveness ratio (ICER). An ICER provides a cost per clinical outcome or QALY.

The aim of this study was to measure, model, and compare the medical costs and HRQL impacts of epilepsy surgery versus continued medical treatment with AEDs for children with DRE.

2. Methods

2.1. Patients

The study sample consisted of 105 children with DRE who underwent epilepsy surgery at the Royal Children's Hospital (RCH) Melbourne between January 2013 and June 2015 and were part of a microcosting study of epilepsy surgery. They had DRE of variable duration, with etiologies including cortical dysplasia in 59, tuberous sclerosis in 17, developmental tumor or cavernoma in 16, and encephaloclastic lesions in 13. Significant comorbidities such as intellectual disability, autism spectrum disorder, and cerebral palsy were present in 38 patients. The patients were aged 0.5 to 18.7 years at the time of surgery (median: 7.6, interquartile range (IQR): 9.2).

2.2. Economic model

A decision analytic model was created to estimate the cost-effectiveness of epilepsy surgery relative to continued medical treatment with AEDs. The model focused on the following outcomes in the surgical treatment group: seizure freedom without AEDs, seizure freedom with AEDs, or persisting seizures, and calculated the difference in costs and outcomes following surgery. Patients who required further surgery continued moving through the model and faced the same possible outcomes up until their fourth surgery. Patients in the medical treatment group continued taking AEDs and remained in the persistent seizure health state or achieved seizure freedom for 12 months before reverting to the persisting seizures health state. TreeAge Pro (TreeAge Pro 2017, R2.1. TreeAge Software, Williamstown, MA, USA) was utilized to construct the decision tree model (Fig. 1).

The time horizon was designed to capture the initial surgery and up to three subsequent surgeries if these were required. Based on economic outcome period data collected from the RCH study sample, the average time from the initial surgery to the second surgery was 2.4 years, from the second to the third surgery was 2.2 years, and from the third to the fourth surgery was 3 years, giving a total average length of follow-up of 7.6 years.

The analysis was undertaken from the perspective of the Australian healthcare system.

2.3. Details of intervention and control

Prior intracranial electroencephalogram (EEG) monitoring, during the same admission and counted as one, epilepsy surgery was performed in 10 surgeries. The surgical procedures performed were uniregional lesionectomies, corticectomies or lobectomies in 99, and multilobar or hemispheric resections or disconnections in the remainder. Postoperative complications included status epilepticus following 8 surgeries, hydrocephalus requiring shunting following one, intracranial hemorrhage following one, and metabolic derangement requiring intensive care unit (ICU) admission following one.

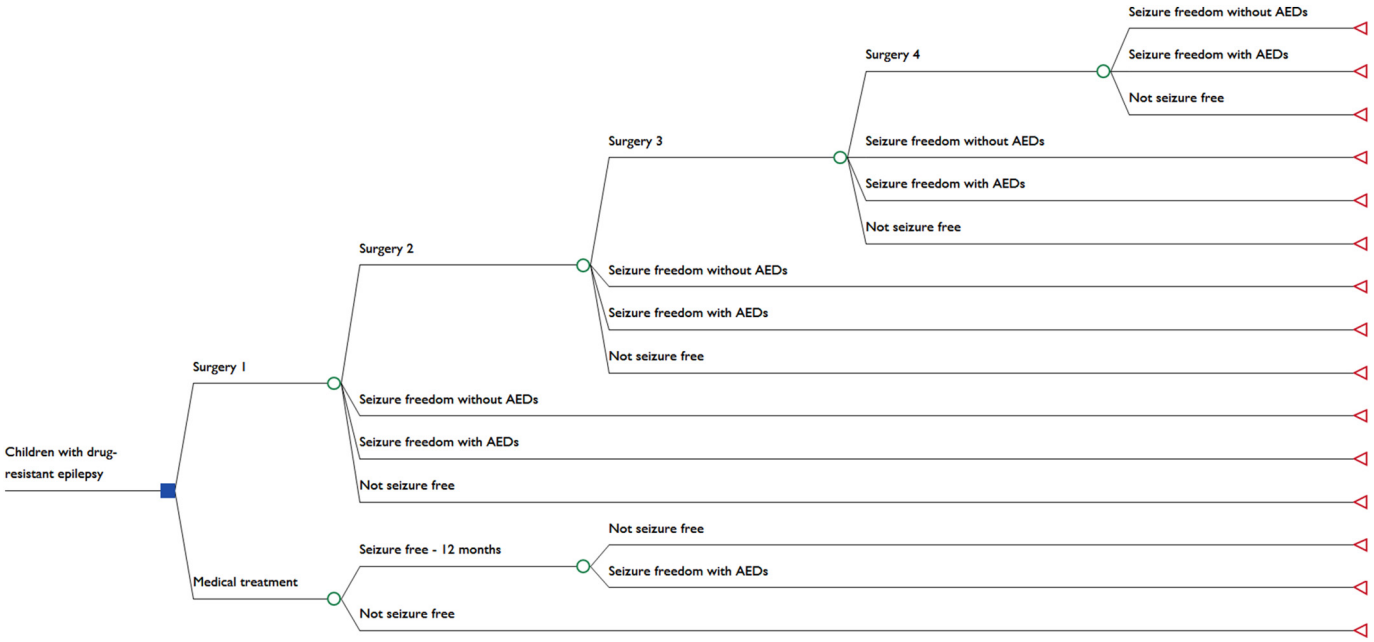

Fig. 1. Decision tree of epilepsy surgery and medical treatment for children with DRE.

Thirty-nine children had more than one epilepsy surgery before, during, or in the 12 months following the microcosting study, for persistent or recurrent seizures; 24 underwent two surgeries, 11 underwent three surgeries, and 4 underwent four surgeries.

Effectiveness data for the medical treatment group were sourced from a single-center trial [16]. Following a review of the literature, this study was selected to inform the medical treatment group parameters for its closeness to the patient group undergoing epilepsy surgery. The patients had drug responsive and resistant forms of epilepsy, and the age range was similar (0.8 to 17.0 years) to the observed surgical group. In the trial, patients were randomized to surgery with appropriate medical therapy or to receive medical therapy alone.

2.4. Clinical outcomes

The study sample was used to calculate the probabilities for patient seizure freedom and ongoing medication status (Table 1). By June 2016, the mean follow-up from first surgery, including surgery prior to the microcosting period, was 3.1 years (minimum 1 year, max 15 years); 51 patients were seizure-free off medication, 16 were seizure-free on medication, and 38 had ongoing seizures.

The probability of attaining seizure freedom in the medical treatment group was 7% and was sourced from the Dwivedi et al.'s [16] study and assumed to persist for 12 months in line with the length of reported study outcomes. After 12 months, 2% of patients remained seizure-free, otherwise returned to the persisting seizures health state (Table 1).

In the absence of published utility values for pediatric patients with epilepsy and ethical approval to contact patients directly, health state valuation for the economic model was performed by an epileptologist, a neurologist, an epilepsy nurse, and a psychologist. They completed the Child Health Utility 9 Dimension (CHU9D) [19] assessment from the perspective of a 10-year-old child of normal abilities in each of the three health states (seizure freedom without medication, seizure freedom with medication, or persisting seizures) one-year postepilepsy surgery. The mean utility scores for each health state are listed in Table 1.

2.5. Resource use and cost estimation

Direct epilepsy surgery costs were collected from a microcosting study of surgeries performed during the 30-month costing study. Hospital costing data provided by central accounting were obtained, verified, and where necessary, adjusted or supplemented for actual activity and consumption related to each patient's surgical admission. Costs of epilepsy surgery included in the analysis were those related to preoperative coordination, surgical planning, anesthesia, operation, intraoperative EEG monitoring, pathology, postoperative care, management of complications including rehabilitation and readmission, and postoperative review over 3 months. The costs of the presurgical workup were not included, and unrelated medical costs during the surgical admissions were removed. To minimize variation within the cost estimates, the sample was bootstrapped 1000 times, and the bootstrapped mean cost was then used for all participants in the economic model. The cost of conducting epilepsy surgery calculated in 2018 dollars was AU $61,417 as listed in Table 1.

The costs of continuing medical treatment were sourced from the literature and included hospitalization, AED treatment, ancillary treatment, rehabilitation, outpatient treatment, auxiliary material, diagnostics, and nursing costs [20]. These medical costs were applied to both treatment groups. The cost of conducting standard medical treatment and management was calculated as AU $11,051 (Table 1).

Table 1
Model inputs: transition probabilities, costs, and utilities.

Variable description	Mean	Distribution	Source
Probabilities (SE)			
Probability of achieving seizure freedom in medical treatment group 1st year	0.07 (0.01)	Beta	Dwivedi 2017
Probability of maintaining seizure freedom in medical treatment group	0.02 (0.02)	Beta	Expert opinion
Probability of having the 2nd surgery	0.37 (0.05)	Beta	Victoria 2014 patient cohort
Probability of seizure freedom and off medication after the 1st surgery	0.37 (0.05)	Beta	Victoria 2014 patient cohort
Probability of seizure freedom and on medication after the 1st surgery	0.08 (0.03)	Beta	Victoria 2014 patient cohort
Probability of remaining seizing after the 1st surgery	0.18 (0.04)	Beta	Victoria 2014 patient cohort
Probability of having the 3rd surgery	0.38 (0.08)	Beta	Victoria 2014 patient cohort
Probability of seizure freedom and off medication after the 2nd surgery	0.18 (0.06)	Beta	Victoria 2014 patient cohort
Probability of seizure freedom and on medication after the 2nd surgery	0.13 (0.05)	Beta	Victoria 2014 patient cohort
Probability of remaining seizing after the 2nd surgery	0.31 (0.07)	Beta	Victoria 2014 patient cohort
Probability of having the 4th surgery	0.27 (0.11)	Beta	Victoria 2014 patient cohort
Probability of seizure freedom and off medication after the 3rd surgery	0.2 (0.1)	Beta	Victoria 2014 patient cohort
Probability of seizure freedom and on medication after the 3rd surgery	0.2 (0.1)	Beta	Victoria 2014 patient cohort
Probability of remaining seizing after the 3rd surgery	0.33 (0.12)	Beta	Victoria 2014 patient cohort
Probability seizure freedom and off medication after the 4th surgery	0.5 (0.22)	Beta	Victoria 2014 patient cohort
Probability seizure freedom and on medication after the 4th surgery	0.00	Beta	Victoria 2014 patient cohort
Probability of remaining seizing after the 4th surgery	0.5 (0.22)	Beta	Victoria 2014 patient cohort
Costs (SD)			
Treatment/management epilepsy both treatment groups (annual)	$11,051 (7278)	Gamma	Riechmann et al. (2015)
Epilepsy surgery	$61,417 (3619)	Gamma	Victoria 2014 patient cohort
Seizure freedom off medication (annual)	$3760 (2164)	Gamma	Riechmann et al. (2015)
Seizure freedom on medication (annual)	$4519 (2437)	Gamma	Riechmann et al. (2015)
Remaining seizing (annual)	$16,607 (9770)	Gamma	Riechmann et al. (2015)
Utilities (SD)			
Seizure freedom off medication	0.92 (0.05)	Beta	Expert opinion
Seizure freedom on medication	0.85 (0.05)	Beta	Expert opinion
Remaining seizing	0.71 (0.05)	Beta	Expert opinion

Prices were adjusted from 2011 Euros to 2018 Australian Dollars by using the average Consumer Price Index (CPI) in 2011 (95) and in 2018 (104) in the Euro Area to generate the conversion factor (1.09). The average general CPI values were obtained from Trading Economics website. The prices in Euros were then converted to Australian Dollars by multiplying each cost with the Euros to Australian Dollars conversion factor (1.62). The conversion factor was generated by Google Finance.

2.6. Ethics approval

This study received ethics approval from The Royal Children's Hospital Melbourne Human Research Ethics Committee (#36155A).

2.7. Analysis and sensitivity analysis

Costs and QALYs were discounted at a rate of 5% per annum [21]. The costs of the intervention (surgery or continued medical treatment) were added to the ongoing costs associated with outcomes for each study arm. Seizure freedom outcomes were calculated along with QALYs for each outcome. The ICER was calculated as follows:

$$\text{ICER} = \frac{\textit{Cost Surgery} - \textit{Cost Medical Treatment}}{\textit{Outcome with Surgery} - \textit{Outcome with Medical Treatment}}$$

The analysis presents two results: firstly, cost per additional patient who achieves seizure freedom in the surgical group compared with the medical group and secondly, cost per QALY gained over the 7.6 years of follow-up.

One-way sensitivity analysis for different probabilities, surgical and medical costs, and discount rates was conducted to assess the impact of uncertainties around the inputs (Appendix A).

Probabilistic sensitivity analysis (PSA) was performed using values and distributions described in Table 1. Monte Carlo simulation was run by applying 10,000 samples.

3. Results

The results of the cost-effectiveness analysis are presented in Table 2. The costs for the epilepsy surgery group over the 7.6 years of follow-up were AU $219,297 compared with AU $170,583 in the medical treatment group. The incremental cost per patient achieving seizure freedom was calculated for the surgical group relative to the medical group. There was a 64% increase in the proportion of patients who achieved seizure freedom over the 7.6 years of follow-up in the surgical group compared with the medical group. The resulting ICER was AU $76,538 per additional patient to achieve seizure freedom in the surgical group compared with the medical group.

The mean QALYs resulting from epilepsy surgery was 5.06, while for a patient who had continued medical treatment it was 4.41 QALYs. The cost per additional QALY gained was, therefore, AU $75,541 for epilepsy surgery compared with continued medical treatment over the 7.6 year follow-up period.

Table 2
Cost-effectiveness analysis results.

	Surgery	Medical treatment
Base case analysis		
Cost	$219,297	$170,583
Seizure freedom	64%	0%
ICER per patient seizure freedom	$76,538	
QALY	5.06	4.41
ICER per QALY	$75,541	
Mean from 10,000 Monte Carlo simulations		
Cost[a]	$218,344 ($53,496)	$169,017 ($73,939)
QALY	5.06 (0.20)	4.41 (0.31)
ICER per QALY	$75,887	

[a] (Standard deviation).

3.1. Sensitivity analysis

The results of one-way sensitivity analyses are presented in Fig. 2 and Appendix A. The model was most sensitive to the utility values for seizure freedom without AEDs and persisting seizures. When the utility value for persistent seizures was lowered to 0.70, the surgical intervention became cost-effective. Surgical intervention also became cost-effective when the cost of epilepsy surgery fell to below $50,220.

The results generated from Monte Carlo simulation including the resulting ICER for cost per additional QALY are presented in Table 2 and Fig. 3. The cost-effectiveness acceptability curves show a 73% probability that the ICER is greater than AU$ 50,000 per additional QALY (Fig. 4).

4. Discussion

This economic evaluation of surgery for DRE in children, incorporating outcomes beyond 12 months, repeat surgeries, and HRQL impacts, showed that the epilepsy surgery was more expensive than continued medical treatment with AEDs over 7.6 years of follow-up (AU$ 219,297 vs AU$ 170,583). Although epilepsy surgery was costlier, it was considerably more effective in terms of patients achieving seizure freedom (64% vs 0%) and QALYs gained (5.06 vs 4.41). A QALY gain of 0.65 equates to an additional 7.8 months of life in full health.

A cost-effectiveness analysis of pediatric epilepsy surgery in Canada, from a tertiary healthcare perspective, also found that although surgery was more costly, it was also more effective [22]. The total direct costs for surgical treatment were twice the costs of medical treatment (CAD$ 30,664 vs CAD$ 15,085). Despite the higher costs, patients who had surgery achieved, on average, a 42% greater reduction in seizure frequency compared with the medical group. The ICER for the surgical group relative to the medical treatment group was CAD$ 369 per 1% seizure reduction. The authors concluded that epilepsy surgery was cost-effective and that their results were consistent with similar studies in children and adults [23–25].

Both our analysis and the Canadian analysis employed a decision tree model; however, the Canadian study incorporated mortality status in the model and focussed on the outcome of seizure reduction, whereas our model focussed on seizure freedom and QALYs. Previous research suggests that HRQL gains primarily occur in patients who achieve seizure freedom and not those who experience a seizure reduction [26]. Importantly, our study modeled reoperation and average time between surgeries, and incorporated longer follow-up (7.6 years compared with one year). For these reasons, our costings are likely to be more comprehensive.

The base case ICER is above the established AU$ 40,000–70,000 cost-effective threshold observed in Australian health economic literature [27], although this threshold is usually applied to results modeled across lifetime follow-up. The current ICER of AU$ 75,541 would likely be reduced when modeled to full life expectancy. Research suggests that the benefits from epilepsy surgery are often not realized for many years [28]. While a lifetime horizon is preferred, there is currently no longer term data on pediatric patients with epilepsy to inform such a model. This study adds to existing literature that has only modeled pediatric patients with epilepsy across a time horizon of 12 months [22].

A further reduction in the ICER is likely if broader effects were incorporated, such as improved patient's participation in school education and employment as well as improved carer outcomes and reduced carer costs. A study in England estimated that the costs for managing childhood epilepsy incurred by education and social care sectors were four times the costs incurred by the health sector [29]. Patients' underproductivity in adult life was found to be the major contribution of the epilepsy burden of disease cost estimates [30]. Moreover, various literatures have indicated the higher unemployment rate among population with epilepsy compared with general population [31,32].

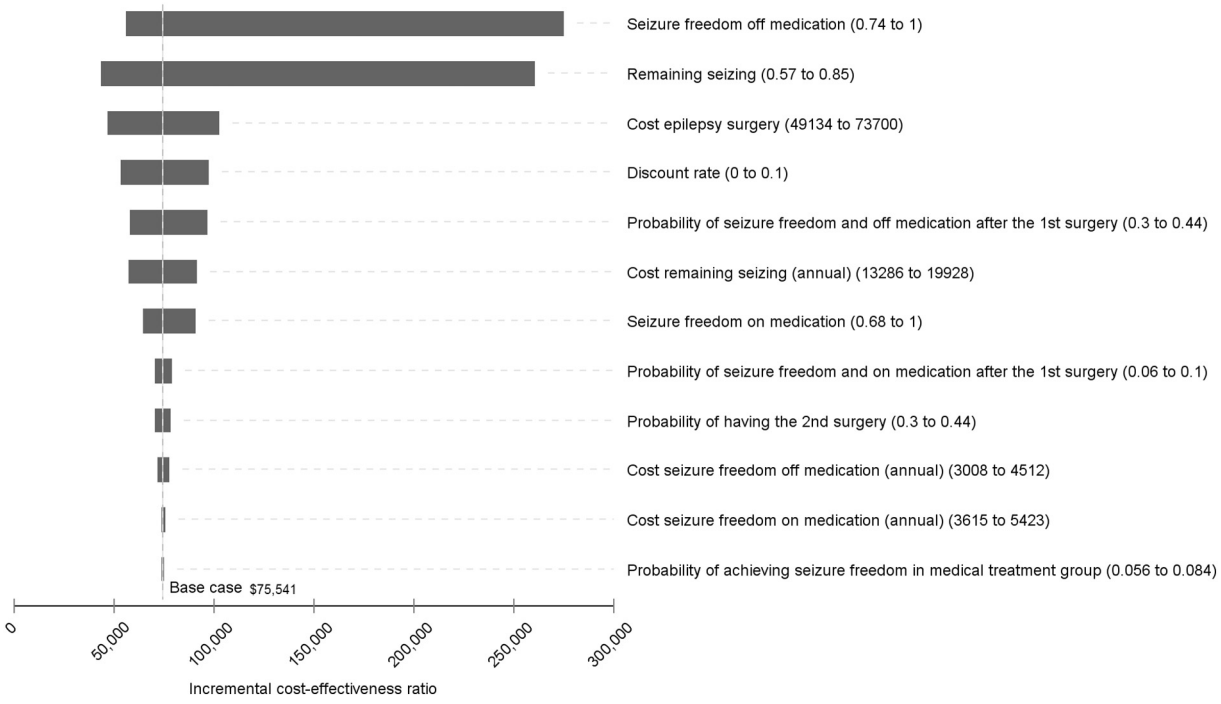

Fig. 2. Tornado plot of the results of the univariate sensitivity analysis. Vertical line is at AU$ 75,541 per QALY and represents the base-case analysis. Refer to sensitivity analysis Appendix A for actual values.

In addition, the measurement of HRQL gains in the current study was narrowly captured and could be greater as the child ages. The incorporation of these potential benefits and reduced costs over a longer time would produce a significantly lower ICER and likely cost-effective result. Future studies could seek a broader evaluation perspective and quantify the benefits and costs of epilepsy surgery from a societal perspective.

Another strength of our model was the use of patient level data for both costs and outcomes. Using patient level data allows for more accurate and representative results. This analysis also took into consideration the postoperative AED status of patients who achieved seizure freedom, something that previous cost-effectiveness analyses ignored.

There were several limitations relating to the availability of some data inputs for the economic model. The costs included did not incorporate those which were not related to surgery, such as preoperative workups required to select surgery candidates and rehabilitations cost for some patients. Individual patient level data for the medical treatment control group were not available and were, therefore, sourced from published studies of comparable populations with DRE. The costs of medical treatment were also sourced from the literature. One-way sensitivity analyses were conducted to assess data uncertainties for these parameters and to test the robustness of the results. The economic model was most sensitive to utility values, highlighting the importance of this area of research as a future priority. The model was also sensitive

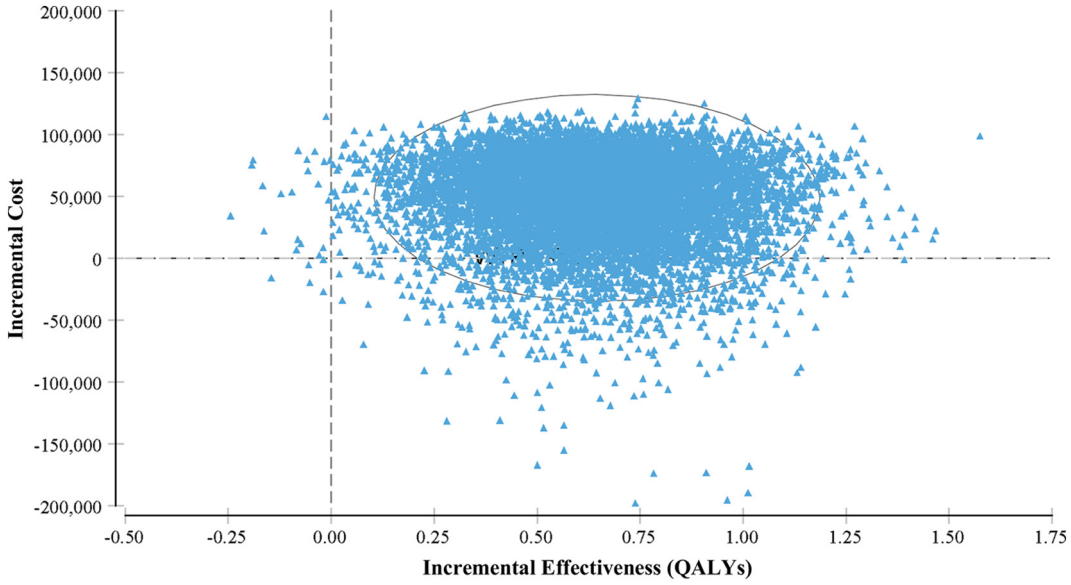

Fig. 3. Scatterplot for probabilistic sensitivity analysis comparing epilepsy surgery relative to medical treatment. The x-axis measures effectiveness in QALYs, and the y-axis measures costs in $AU.

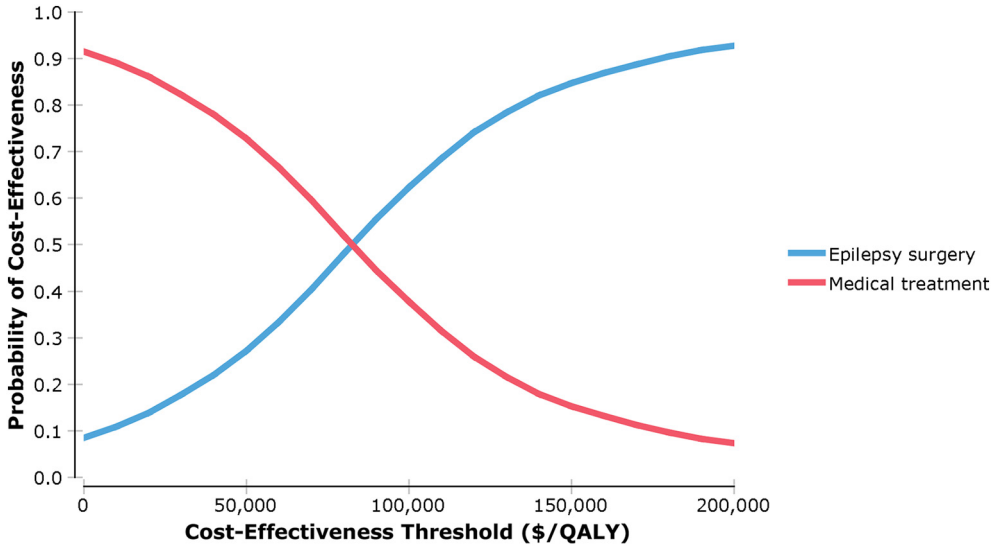

Fig. 4. Cost-effectiveness acceptability curve illustrating the probability of cost-effectiveness of epilepsy surgery relative to medical treatment for a given cost-effectiveness threshold value.

to parameters for which original data were available (costs of surgery and outcomes following first surgery).

The economic evaluation reflects the heterogeneity of the patient group that may limit the generalizability of findings. The study sample incorporated an age range of 0.5 to 18.7 years, and patients had different types of epilepsy etiologies that required individualized surgical approaches. Consequently, the cost and outcomes calculated across the modeled time horizon may not well represent any one subgroup.

5. Conclusion

Given the length of time that children who suffer from DRE live with the condition, it is important that cost-effectiveness results are available to inform resource allocation decisions. Our findings suggest that epileptic surgery is significantly more expensive than AEDs but also more effective. More accurate measurements of HRQL and a longer study timeframe are needed to validate our findings. The inclusion of benefits outside the healthcare perspective would also likely lead to a more compelling cost-effective argument.

Conflict of interest

The authors declare no conflict of interest.

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Appendix A. One-way sensitivity analyses for variation in surgical and medical treatment outcomes

Parameters	Base-case value	Test value	ICER seizure-free patients	ICER QALY
Base case			$76,538	$75,541
Costs				
Epilepsy surgery	$61,417	$49,134–$73,700	$47,623–104,157	$47,490–$103,505
Seizure freedom off medication health state (annual)	$3760	$3008–$4512	$72,802–78,978	$72,429–$78,566
Seizure freedom on medication health state (annual)	$4519	$3615–$5423	$74,936–76,844	$74,585–$76,410
Persistent seizures health state (annual)	$16,607	$13,286–$19,928	$58,754–93,026	$58,604–$92,391
Discount rate	5%	3.5%–10%	$67,593–81,565	$54,298–$98,566
Utilities				
Seizure freedom off medication	0.92	0.74–1	NA	$56,919–$284,267
Seizure freedom on medication	0.85	0.68–1	NA	$65,570–$91,136
Remaining seizing	0.71	0.57–0.85	NA	$44,095–$262,282
Probabilities				
Seizure freedom in AED group	0.07	0.06–0.08	$75,577–$76,204	$74,979–$76,019
Seizure freedom and off meds 1st surgery	0.37	0.3–0.44	$60,518–$95,048	$58,147–$97,345
Seizure freedom and on meds 1st surgery	0.08	0.06–0.1	$71,308–$80,769	$70,759–$79,436
Second surgery	0.37	0.3–0.44	$73,628–$77,911	$70,838–$78,876
Annual cost $AUD2018				

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