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RESEARCH ARTICLE

Economic evaluation of deep brain stimulation compared with vagus nerve stimulation and usual care for patients with refractory epilepsy: A lifetime decision analytic model

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Abstract

Objectives: This study was undertaken to estimate the cost-effectiveness of deep brain stimulation (DBS) compared with vagus nerve stimulation (VNS) and care as usual (CAU) for adult patients with refractory epilepsy from a health care perspective using a lifetime decision analytic model.

Methods: A Markov decision analytic model was constructed to estimate the lifetime cost-effectiveness of DBS compared with VNS and CAU. Transition probabilities were estimated from a randomized controlled trial, and assumptions were made in consensus with an expert panel. Primary outcomes were expressed as incremental costs per quality-adjusted life-year (QALY) and per responder. Univariate and probabilistic sensitivity analyses were conducted to characterize parameter uncertainty.

Results: In DBS, 28.4% of the patients were responders, with an average of 21.38 QALYs per patient and expected lifetime health care costs of €187 791. VNS had fewer responders (22.3%), fewer QALYs (20.70), and lower lifetime costs (€156 871). CAU had the fewest responders (6.2%), fewest QALYs (18.74), and lowest total health care costs (€64 670). When comparing with CAU, incremental cost-effectiveness ratios (ICERs) showed that costs per QALY gained were slightly lower for DBS (€46 640) than for VNS (€47 155). When comparing DBS with VNS, an incremental cost per additional QALY gained of €45 170 was found for DBS. Sensitivity analyses showed that ICERs were heavily dependent on assumptions regarding loss to follow-up in the respective clinical trial.

Significance: This study suggests that, given current limited evidence, VNS and DBS are potentially cost-effective treatment strategies compared to CAU for patients with refractory epilepsy. However, results for DBS were heavily impacted by assumptions made to extrapolate nonresponse from the original trial. More stringent assumptions regarding nonresponse resulted in an ICER just above an acceptable willingness to pay threshold. Given the uncertainty surrounding the

effectiveness of DBS and the large impact of assumptions related to nonresponse, further empirical research is needed to reduce uncertainty.

KEYWORDS

antiseizure medication, deep brain stimulation, Markov model, refractory epilepsy, vagus nerve stimulation

1 | INTRODUCTION

Approximately 30% of patients with epilepsy are not seizure-free while on antiseizure medications (ASMs).[1] Those with uncontrolled seizures and in whom two or more adequately dosed ASMs have failed are commonly referred to as having refractory epilepsy and may be candidates for resective epilepsy surgery. For those who are not eligible for resective epilepsy surgery or continue to have seizures after surgery, two neuromodulation options are available that can be provided concomitant to ASMs: vagus nerve stimulation (VNS) and deep brain stimulation (DBS).[2]

VNS and DBS are neurostimulators that act as alternative treatments to ASMs for patients with refractory epilepsy. Both are battery-powered devices and send regular electrical pulses to specific parts of the brain to counteract the irregular electrical brain activities that cause seizures and are placed by neurosurgeons during surgery under general anesthesia. The VNS stimulator is implanted subcutaneously into the upper part of the chest, where electrical stimulation is sent through an electrode that is attached to the vagus nerve, one of the largest cranial nerves.[3,4] DBS sends electrical impulses that travel through electrodes to the anterior nucleus of thalamus, a part of the brain that is involved in the spread of seizures.[5,6]

VNS has been approved to be used in clinical practice in Europe since 1994 and in the United States since 1997.[7] Since then, its efficacy has been demonstrated by two randomized, double-blind, active-controlled trials[8,9] and a prospective long-term study of its safety.[10] In 2010, DBS was approved by the European Medicines Agency after publication of the results of the Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy (SANTE) trial, a prospective, multicenter, double-blind, randomized controlled trial (RCT) that evaluated the use of DBS therapy for patients with refractory epilepsy with partial onset seizures.[11] In the United States, approval was granted by the US Food and Drug administration in 2017.[12] However, market approval does not necessarily mean use in clinical practice, which is often dependent on reimbursement decisions. Nowadays, economic evaluations are commonly conducted to aid policy-makers in making reimbursement and pricing decisions. Such health economic evidence for

Key Points

- Given the current (limited) evidence, DBS and VNS are potentially cost-effective treatment strategies compared to CAU for patients with refractory epilepsy
- Incremental cost-effectiveness ratios for DBS compared to CAU heavily depend on assumptions regarding loss to follow-up in clinical trials
- When it is assumed that all patients without follow-up data in the SANTE trial discontinued treatment, the ICER for DBS substantially increases
- In the case that WTP thresholds fall below €44 000 per QALY gained, CAU is the preferred option in all analyses
- Given the absence of long-term data, (short-term) trial data were extrapolated to predict lifetime outcomes without treatment waning for all treatment arms

DBS is, however, lacking in the published literature. This gap of knowledge has been highlighted by the latest systematic review about economic evaluations of treatments for patients with epilepsy.[2,13]

Decision analysis is a systematic and quantitative approach that serves as a valuable guide for decision-makers in their decision-making, especially when there is uncertainty regarding one or more key parameters.[14,15] A decision analytic model combines data from multiple sources (i.e., original data, published literature, and expert opinion) to derive outcome-related probabilities and may serve as a simplification of reality.[16] For each intervention, costs and effects (in terms of quality-adjusted life-years [QALYs]) are associated with those outcomes.[14] Due to the lack of trial data to compare long-term incremental (cost-)effectiveness between DBS, VNS, and care as usual (CAU), a decision analytic model is needed and act as an ideal instrument to acquire a realistic impression of how long-term cost-effectiveness of DBS would be compared to the current epilepsy treatments (i.e., VNS and CAU).

Therefore, the objective of this study was to estimate the cost-effectiveness of DBS compared with VNS and CAU for adult patients with refractory epilepsy from a health care perspective using a lifetime decision analytic model.

2 | MATERIALS AND METHODS

This study was performed and reported following the CHEERS (Consolidated Health Economic Evaluation Reporting Standards) statement and guidelines for good practice in decision analytic modeling in Health Technology Assessment.[17,18]

2.1 | Target population

The target population was patients with refractory epilepsy with uncontrolled seizures in whom two or more adequately dosed ASMs had failed and who were not eligible for resective epilepsy surgery or continued to have seizures after surgery. Patients entered the model at a starting age of 35 years (in accordance with the mean of the population included in the study of Fisher et al.[11]).

2.2 | Decision model

A probabilistic Markov cohort simulation model was used to simulate a hypothetical cohort of patients followed over time, which served to estimate the prognosis of each intervention to evaluate the cost-effectiveness of DBS compared with VNS and CAU. A Markov decision analytic model consists of a finite number of discrete mutually exclusive "health states" that are connected by "transitions" that correspond to clinically important events, representing the disease progress, each associated with costs and outcomes (e.g., quality of life).[19] Transition probabilities express the likelihood for a patient to transit from one health state to another.[20–22] Based on those probabilities, costs, and effects, cost-effectiveness can be calculated for each comparison of interventions for the desired time period. A Markov cohort was chosen given the lack of available data. A patient-level simulation (i.e., including individual patient characteristics) may be considered a more realistic representation of reality. However, such a model would require a vast amount of (individual-patient level) information, which was not available to us. Furthermore, the Markov model approach has previously been applied within epilepsy.[23]

The model was established using Excel 2010 software package (Microsoft). It was run up to a time horizon of 70 years (assumed to be lifetime given the starting age of

35 in the model), from the health care perspective (i.e., including health care costs only without considering costs to society as a whole, such as productivity losses). To get insight into our input parameters, we performed an extensive search on published literature. Additionally, a panel of experienced neurologists ($n = 5$), neurosurgeons ($n = 4$), and Health Technology Assessment experts ($n = 2$) was consulted through individual interviews. During these, each expert was asked to provide feedback and to validate the model structure, input parameters, model assumptions, and estimates of transition probabilities. As a result, the final model consisted of four health states—no improvement (NOIM), improvement (IMPR; defined as having ≥50% seizure reduction), seizure-free (SF), and death (D; all-causes)—and nine transition probabilities (Figure 1). All patients entered the Markov model as NOIM and from there, patients could transit to IMPR, SF, or D, or stay in NOIM after each cycle of 3 months. The cycle length of 3 months was chosen to be in line with the follow-up length of the SANTE trial. The health state D acted as an absorbing health state where patients who entered will always remain in that state. Outcomes for this study were (incremental) costs per QALY[14] and incremental costs per responder, where responder was defined as ≥50% reduction in seizure frequency, in line with previous health economic models in epilepsy.[24]

2.3 | Parameters

2.3.1 | Transition probabilities, health state utilities, and adverse events

Following a systematic literature search (see Table S3) and expert meetings, we derived probability estimates for transitions, efficacy, and safety for DBS from the SANTE RCT[11] and the corresponding long-term follow-up study (see Table S1).[25] Similarly, two RCTs that compared VNS with CAU[8,9] and one long-term trial[10] were found for VNS. As for CAU, we used data from the control arms of three RCTs and one economic evaluation to estimate its transition probabilities.[11,26–28] For cycles for which evidence from multiple sources was available, pooled estimates were made using a meta-analytic fixed-effect model.[29] For those parameters, we employed beta uncertainty distributions. In addition, the 3-month mortality rate was adjusted for age using the annual age-specific all-cause mortality rates available from Statistics Netherlands.[30]

As adverse events, the probability of postimplantation infection due to DBS or VNS implantation was included. These included antibiotic treatment with removal and/or replacement of the devices. This probability was estimated to be 12.7% for DBS[11] and 2% for VNS.[9] The costs
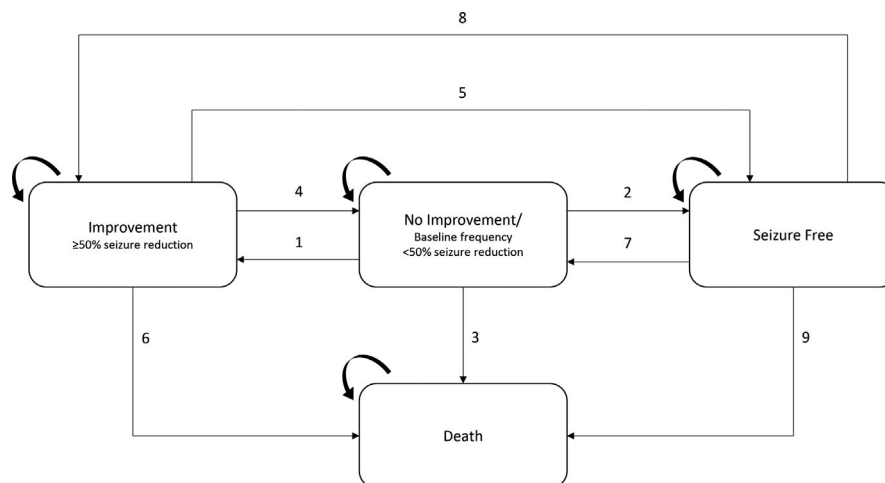
FIGURE 1 The Markov model. (1) Probability of improvement for no improvement patients. (2) Probability of seizure-free for no improvement patients. (3) Probability of death for no improvement patients. (4) Risk of no improvement for improvement patients. (5) Probability of seizure-free for improvement patients. (6) Probability of death for improvement patients. (7) Probability of no improvement for seizure-free patients. (8) Probability of improvement for seizure-free patients. (9) Probability of death for seizure-free patients

associated with these infections were included in the model (see below), but no utility decrement was applied, given that these adverse events generally do not result in chronic utility decrement. Probabilities of adverse events were considered for initial implementation of DBS and VNS and for each consecutive battery replacement. In the SANTE trial, there were no symptomatic or clinically significant hemorrhages. Therefore, stroke was not included as an adverse event in the model.

The primary data source for effectiveness data for DBS was the SANTE trial. However, in the SANTE-trial, 5-year follow-up was obtained from only 59 patients of the original 109 (randomized) patients, of whom 83 patients were still on active treatment at 5-year follow-up. Hence, following intention-to-treat principles, the proportion of patients in each health state was adjusted for the number of patients with treatment discontinuation, assuming a total of 83 patients at 5-year follow-up, of whom the patients whose health status was not assessed at 5 years $(83 − 59 = 24)$ were assumed to have the same efficacy as those who were measured at 5 years. This assumption was subjected to a sensitivity analysis in which all patients whose health status was not assessed at 5 years were assumed to have discontinued treatment, resulting in a total of 59 patients still on active treatment at 5-year follow-up, of the original 109 randomized patients.

For each treatment in the model, transition probabilities were estimated for cycles up until evidence was available, after which patients were assumed to stay in the same health state for the rest of the time horizon (except for background mortality). For DBS, this meant that evidence was available until Cycle 20 (5-year follow-up), for VNS this meant that evidence was available until Cycle

6 (1.5-year follow-up), and for CAU this meant that evidence was only available for the first cycle (3-month follow-up; in line with the duration of the time spent in the control group in the SANTE trial). Transition probabilities (per cycle) are presented in Table S1.

2.3.2 | Costs and effects

Costs and effects (e.g., QALYs) were incorporated into the model as mean values per health state for each cycle. Costs were converted to 2017 Euros using consumer price indexed from Statistics Netherlands.[31] Both costs and effects of each intervention were based on literature, maximum tariffs from the Dutch National Health Care Institute,[32] and expert opinion (e.g., the resource use for the three treatments was based on clinical guidelines and expert opinion, which was used to determine overall treatment costs). Costs for implantation of VNS and DBS derived from the Dutch Health Care Authority were, according to consultation with experts, considered acceptable approximates. VNS- and DBS-related infection costs were derived from Wetzelaer et a.[33] In addition, average infection-related costs and costs of withdrawals were calculated according to the rates of treatment options chosen, provided, and agreed by experts. Other health care costs (e.g., visits with neurologists, visits with nurse practitioner) were derived from the Dutch manual for costing studies in health care.[32] It was assumed that, based on expert opinion, the average lifespan of the neurostimulator until surgery is required to replace either the batteries or the neurostimulator as a whole was every 5 years. These costs were included in

the model for both DBS and VNS including infection-related costs and cost of withdrawals.

During our expert meeting, we decided to follow the recommendation of de Kinderen et al.[23] to use the utility values of Maltoni and Messori,[26] as the health states described in this paper are best matched to the health states in our model. From these utility values, QALYs were calculated by multiplying the time spent in a health state by the utility of that health state (see Supplementary Material S1). The expected future costs were discounted to present values using the annual discount rate of 4.0% and 1.5% for the effects, as recommended by the Dutch guidelines for pharmacoeconomic research.[32] We applied the beta distribution to describe uncertainty around the effect parameters.

2.4 | Cost-effectiveness analysis

First, incremental costs and effects of each intervention under evaluation (i.e., DBS, VNS, and CAU) were calculated based on the mean costs and effects values over the whole time horizon. Then we calculated the incremental cost-effectiveness ratio (ICER) as follows: ICER = (expected cost$_A$ − expected cost$_B$) / (expected effects$_A$ − expected effects$_B$), where the subscripts A and B refer to the intervention DBS, VNS, or CAU. The ICER was used to estimate the cost-effectiveness of DBS and VNS compared to CAU and of DBS compared to VNS, describing the additional cost per extra QALY gained or cost per additional responder between treatments. The ICERs were then plotted onto cost-effectiveness planes (CE-planes). The CE-planes are divided into four separate quadrants and can be interpreted as follows: ICERs in the northeast (NE) or the southwest (SW) quadrants are positive. ICERs in the NE quadrant indicate that the new treatment is thought to be costlier and more effective, and vice versa, new treatment is less costly and less effective than control when the ICER is in the SW quadrant. ICERs in the southeast (SE) and northwest quadrant are negative values. In the SE quadrant, the new treatment is less costly and more effective compared to control. On the opposite side, the new treatment is more costly and less effective compared to the old treatment. In the Netherlands, depending on the burden of disease, the willingness-to-pay threshold for 1 QALY for adoption in the Netherlands varies from €20 000 to €80 000 per QALY.[34] Given the disease burden of refractory epilepsy, a threshold of €50 000 was assumed in this study. If an ICER falls below this threshold, the intervention is considered to be cost-effective (i.e., the additional effects outweigh the additional costs).

2.5 | Deterministic and probabilistic sensitivity analysis

First, deterministic sensitivity analyses were performed in which the effects of a shorter time horizon were examined for a 5-year period, given that the average lifespan of the neurostimulator until surgery is required to replace either the batteries or the neurostimulator as a whole was every 5 years. Next, an analysis was performed in which all patients without follow-up data in the SANTE trial were assumed to have discontinued treatment (intention-to-treat [ITT] restricted scenario). This scenario assumed that given 109 patients were initially randomized in the study, and 5-year follow-up was obtained from only 59 patients, the remaining 50 patients without follow-up were nonresponders at 5-year follow-up. Lastly, given that DBS and VNS were subject to confidential pricing, a scenario was added in which tariffs for noncontracted care were used for both DBS and VNS procedures (see Table S2).

Next, to examine the impact of parameter uncertainty on the modeled outcomes, we performed a probabilistic sensitivity analysis (PSA). In this process, we assigned specific distributions to each input parameter and sampled simultaneously from these probability distributions to evaluate the joint effect of input parameter uncertainty in our decision model (see Supplementary Material S1).[15,35,36] Hence, for transition probabilities and utility values, the beta distribution was used. To capture variability in our cost parameters with the lack of corresponding standard errors due to the use of expert opinion, beta program evaluation and review technique distribution was applied instead of the more common gamma distribution.[16]

The Monte Carlo simulation, which simultaneously draws parameters from probability distributions for each input, was run 1000 times. The resulting ICERs were then plotted onto CE-planes, which are scatterplots that represent uncertainty surrounding the ICER. Results from the PSA were presented in cost-effectiveness acceptability curves (CEACs), which portray the probability that each intervention is cost-effective at a maximum willingness to pay (WTP) for each QALY gained.

3 | RESULTS

3.1 | Base case analysis at lifetime time horizon: ITT

The results of the base case cost-effectiveness analyses are presented in Table 1. In DBS, 28.4% of the patients were responders, with an average of 21.38 QALYs per patient and expected lifetime health care costs of €187 791. VNS had

fewer responders (22.3%), fewer QALYs (20.70), and lower lifetime costs (€156 871). CAU had the fewest responders (6.2%), fewest QALYs (18.74), and lowest total costs (€64 670). When comparing with CAU, ICERs showed that costs per QALY gained were lower for DBS (€46 640) than for VNS (€47 155) compared to CAU. When comparing DBS with VNS, an incremental costs per additional QALY gained of €45 170 was found for DBS. Although there is currently no defined WTP for costs per responder in the Netherlands, the ICERs are presented in Table 1, with an ICER of €506 634 per responder for DBS compared to VNS, €553 860 per responder for DBS compared to CAU, and €571 733 per responder for VNS compared to CAU.

3.2 | Sensitivity analyses at lifetime time horizon: ITT restricted

A sensitivity analysis in which all patients without follow-up data in the SANTE trial were assumed to have discontinued treatment (ITT restricted scenario) resulted in substantially higher ICERs at lifetime than the base case (€65 911 vs. €46 640 per QALY gained, respectively) for DBS compared to CAU (Table 1). When compared to VNS, DBS was dominated in this analysis, with higher costs and lower QALYs.

At 5 years after implantation, 42.2% of the DBS patients were responders, with an average of 3.42 QALYs per patient and expected health care costs of €72 251. VNS had fewer responders (34.4%), had less effect (3.37 QALYs), and was less expensive (€53 940) than DBS. Lastly, CAU had the fewest responders (10.3%) and least effect (3.17 QALYs) and was the least costly (€15 819) of all treatments. Compared to CAU, DBS had an ICER of €221 916 per QALY gained and VNS had an ICER of €183 735 per QALY gained.

When assuming prices based on the tariffs for noncontracted care for both DBS and VNS, a marginally higher ICER compared to the base case was found (€50 021 vs. €46 640 per QALY gained) for DBS compared to CAU (Table 1). When comparing DBS with VNS, an incremental cost per additional QALY gained of €50 874 was found for DBS in this scenario.

3.3 | Probabilistic sensitivity analyses

Results of the PSAs for all three comparisons (DBS-CAU, VNS-CAU, and DBS-VNS) are shown in Figure 2. From the base case, the CEAC shows that assuming a WTP of €50 000, DBS has a 59.0% probability of being cost-effective, compared to 1.0% and 40.0% for VNS and CAU, respectively (Figure 2A,B). At the ceiling ratio of €80 000, DBS, VNS, and CAU had a probability of 87.0%, 1.0%, and 12.0%, respectively, of being cost-effective. Below a WTP of €44 000 per QALY, CAU is the preferred strategy, with

TABLE 1 Results of the base case and sensitivity cost-effectiveness analyses

	Expected cost, €	Expected QALYs	Responders, %	Comparison	ICER, €/QALY	ICER, €/responder
Lifetime, base case						
DBS	€187 791	21.38	28.4%	DBS-VNS	€45 170	€506 634
VNS	€156 871	20.70	22.3%	DBS-CAU	€46 640	€553 860
CAU	€64 670	18.74	6.2%	VNS-CAU	€47 155	€571 733
Lifetime: ITT restricted scenario						
DBS	€191 340	20.66	22.0%	DBS-VNS	−€1 029 909 (dominated)	−€10 924 099 (dominated)
VNS	€156 871	20.70	22.3%	DBS-CAU	€65 911	€801 145
CAU	€64 670	18.75	6.2%	VNS-CAU	€47 155	€571 733
At 5 years						
DBS	€72 251	3.42	42.2%	DBS-VNS	€391 123	€235 956
VNS	€53 940	3.37	34.4%	DBS-CAU	€221 916	€56 432
CAU	€15 819	3.17	10.3%	VNS-CAU	€183 735	€38 121
Using noncontracted care tariffs						
DBS	€196 716	21.38	28.4%	DBS-VNS	€50 874	€570 616
VNS	€161 891	20.70	22.3%	DBS-CAU	€50 021	€594 009
CAU	€64 670	18.74	6.2%	VNS-CAU	€49 722	€602 863

Abbreviations: CAU, care as usual; DBS, deep brain stimulation; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; QALY, quality-adjusted life-year; VNS, vagus nerve stimulation.

a probability of being cost-effective of 51.0%, which increases as WTP decreases.

From the ITT restricted analysis, corresponding probabilities at a WTP of €50 000 were .0%, 55%, and 46% for DBS, VNS, and CAU, respectively (Figure 2C,D), indicating that in the ITT restricted analysis, VNS is preferred over DBS.

The PSA for the shorter 5-year time horizon indicated that CAU is the preferred option, with a 100% and 99% chance of being cost-effective at WTP thresholds of €50 000 and €80 000 per QALY, respectively.

Results based on the tariffs for noncontracted care for both DBS and VNS were similar to the base case analysis; at a WTP of €50 000, probabilities of being cost-effective were 5%, 52%, and 43% for DBS, VNS, and CAU, respectively (Figure 2G,H).

4 | DISCUSSION

The objective of this study was to develop a health economic decision analytic model to estimate the cost-effectiveness of DBS compared with VNS and CAU for adult patients with refractory epilepsy. To our knowledge, this is the first study investigating the cost-effectiveness of DBS in patients with refractory epilepsy using a Markov decision analytic model. Our primary results showed that the expected costs were highest for DBS, then VNS, and lowest for CAU. As DBS and VNS are both invasive procedures with high initial costs compared to CAU, it was expected that DBS and VNS would not necessarily be more cost-effective in the short term compared to CAU as a result of the high initial costs in the first year. Assuming a lifetime time horizon, ICERs showed that costs per QALY gained were slightly lower for DBS (€46 640) than for VNS (€47 155) compared to CAU, with DBS having the highest chance of being cost-effective at WTP thresholds above €50 000 per QALY. However, these results must be seen in light of the limited currently available evidence for especially DBS but also VNS. For example, it is clearly demonstrated that the way treatment discontinuation is handled heavily impacts the ICER. In our base case, we have assumed that the proportion of responders is equal between patients with and without follow-up. When it is assumed that all patients without follow-up data in the SANTE trial discontinued treatment, the ICER for DBS substantially increased, caused by decreased QALY gains, leading to VNS being the preferred strategy and DBS not being cost-effective at a WTP of €50 000 per QALY. Moreover, it should be noted that, in the case that WTP thresholds fall below €44 000 per QALY gained, CAU is the preferred option in all analyses. It is unlikely that, in the Netherlands, WTP thresholds below €44 000 per QALY would be

considered for epilepsy (i.e., given its disease burden), as the cost-effectiveness thresholds range between €20 000 and €80 000 according to disease severity, and epilepsy classifies as a severe disease. However, one should note that WTP thresholds may vary between countries and are generally dependent on the gross domestic product of a country. For example, the World Health Organization recommends a threshold of less than three times the national annual gross domestic product per capita.[37]

It should be emphasized that, whereas the base case analysis (i.e., assuming the proportion of responders is equal between patients with and without follow-up) may be too optimistic, given that it is more likely that patients with a poor response drop out of the study (and hence would result in an overall lower efficacy), the alternative scenario in which all patients without follow-up data are classified as nonresponders may be too pessimistic, as it is likely that being a nonresponder is not the sole reason to drop out of a clinical trial. The true ICER is likely to be somewhere in between the estimates presented in the present study and would still be considered to be an efficient use of health care resources given Dutch WTP thresholds. This is in line with other disease areas. When reviewing studies of DBS for Parkinson disease and obsessive–compulsive disease, a disease area in which DBS has been used for a long period of time, DBS has been shown to be a both clinical and cost-effective surgical intervention.[38–40]

There are several other potential limitations. First, there is a lack of data on the effect of DBS on both seizure frequency and seizure severity in the selected trials that are included for parameter estimation in this study. This is considered to be a drawback because seizure severity is thought to be one of the important determinants for the burden of epilepsy, therefore influencing patients' quality of life.[41] For example, according to our expert panel, the biggest benefit of VNS so far is not necessarily decreasing seizure frequency, but decreasing the severity of seizures. In addition, the economic burden of patients with controlled epilepsy differs from that of patients with refractory epilepsy, but little is known about the specific burden for those treated with VNS or DBS.[27,42,43] Second, short-term trial evidence was extrapolated to a lifetime time horizon. This entailed that patients were not able to transition between health states after the follow-up time of the trial (except when patients died in the model). This should especially be emphasized as no treatment waning was assumed. Hence, it was assumed that at the end of the follow-up of the original trial data, treatment effectiveness remained stable for all arms in the model. Third, in the Netherlands, the Dutch guideline for economic evaluations recommends performing and reporting economic evaluations from a societal perspective. One of the criteria of assessing from a societal perspective is to include all
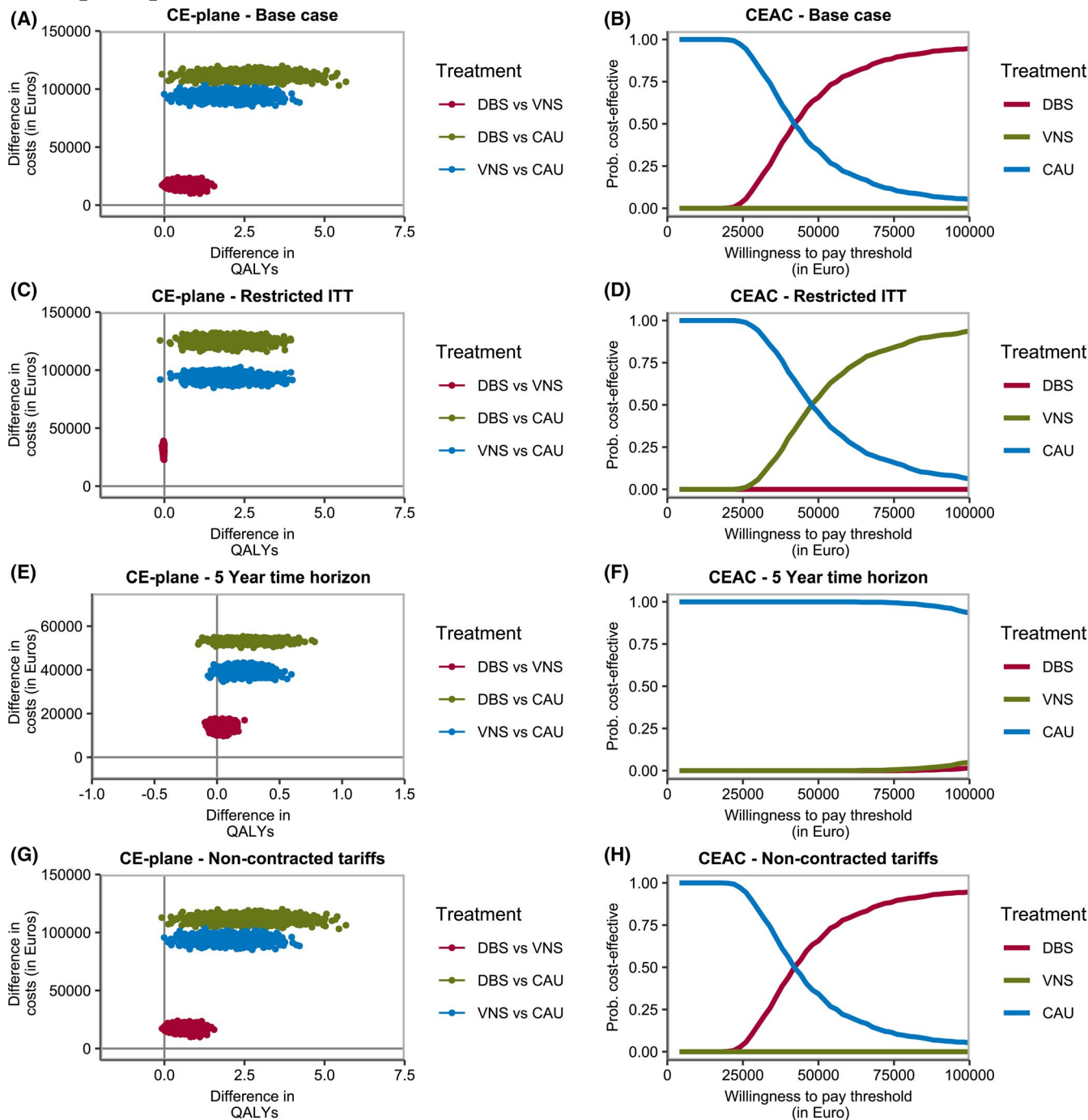
FIGURE 2 Cost-effectiveness planes (CE-planes) and cost-effectiveness acceptability curves (CEACs) of (A, B) base case analysis at lifetime time horizon, (C, D) restricted intention-to-treat (ITT) analysis at lifetime time horizon, (E, F) results of sensitivity analysis assuming a 5-year time horizon, and (G, H) results of sensitivity analysis assuming tariffs for noncontracted care. CAU, care as usual; DBS, deep brain stimulation; QALY, quality-adjusted life-year; VNS, vagus nerve stimulation

costs relevant to society (e.g., productivity losses and informal care). Due to the lack of relevant data in our selected studies, our model is constructed using cost parameters from the Dutch health care perspective only. This likely results in conservative cost-effectiveness estimates considering both DBS and VNS compared to CAU, given that both DBS and VNS demonstrated superior clinical effectiveness,

which would likely result in improved outcomes relevant to society as a whole, such as reduced productivity and reduced need for informal care. Fourth, we had to rely on expert opinion regarding health care resource use for VNS and DBS, instead of observational data, which may have caused overestimation of the true costs. Fifth, although in practice it is possible for patients who are seizure-free

to discontinue pharmacological treatment, this was not included in the model. This could result in a minor over-estimation of health care costs in the CAU health state. However, given that health state-dependent cost estimates were used, we believe the impact of this simplification is likely to be small. Sixth, to be able to include all three treatments in the model, data from multiple studies had to be used. Given that the final choice for DBS, VNS, or CAU is likely to be dependent on various patient characteristics (e.g., etiology, topographical type [focal or generalized epilepsy], age of the patient), it is likely that populations between studies are not fully comparable. However, the latter cannot be easily tackled, given that this would require a randomized study (i.e., in which patients would be randomized between DBS, VNS, and CAU, which would likely be deemed unethical) or alternative approaches using individual patient-level data from previously conducted trials combined with statistical techniques that could (partially) substitute randomization to treatment conditions (i.e., inverse propensity weighting, also known as inverse probability of treatment weighting).[44] Hence, an indirect comparison as was performed in the current study is second best to shed light on the incremental costs and effects associated with each treatment. Finally, in the model it was assumed that patients could be classified as being seizure-free within 1 year after treatment. In practice, patients are frequently only classified as seizure-free when seizures are absent for at least 12 months.

5 | CONCLUSIONS

This study suggests that, given the current limited evidence, DBS and VNS are potentially cost-effective treatment strategies compared to CAU for patients with refractory epilepsy in the Dutch health care system. However, results for DBS were heavily impacted by assumptions made to extrapolate nonresponse from the original trial. More stringent assumptions regarding nonresponse resulted in an ICER just above an acceptable WTP threshold. Given the lack of evidence on the effectiveness of DBS, further empirical research is needed to reduce uncertainty.

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