AN ECONOMIC EVALUATION OF VAGUS NERVE STIMULATION AS AN ADJUNCTIVE TREATMENT TO ANTI-SEIZURE MEDICATIONS FOR THE TREATMENT OF DRUG-RESISTANT EPILEPSY IN ENGLAND

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Objectives

Approximately one in three epilepsy patients fail to produce an adequate response to current anti-seizure medications (ASMs) and are considered to have drug-resistant epilepsy (DRE).[1] This produces an increased burden on these patient's lives, carers and respective healthcare systems. For DRE patients who cannot have surgery, clinical bodies may recommend vagus nerve stimulation (VNS) as a treatment.

The objective of this analysis was to assess the cost-effectiveness of VNS as an adjunctive therapy to ASMs in an English healthcare setting, compared to ASMs alone.

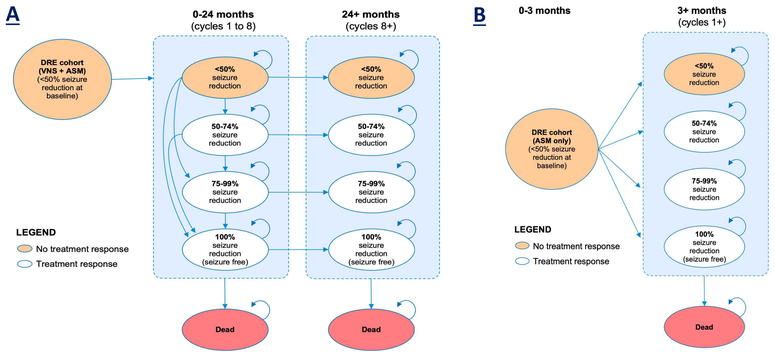
Methods

A cohort Markov state transition model was used to evaluate cost-effectiveness from an English National Health Care (NHS) perspective.

Individual patient-level data from two randomised controlled trials (E03 and E05) studying the efficacy of high versus low stimulation VNS therapy informed population characteristics and the estimates of effectiveness in the model for the first cycle.[2,3]

The model was developed with a three-month cycle length, to match the study durations of the E03 and E05 trials. Health states were defined by percentage reduction in seizure frequency, as illustrated in Figure 1, to coincide with clinical efficacy evidence and previous cost-effectiveness analyses in this therapy area.

Figure 1. Illustration of the model structure of (A) VNS with ASM treatment and (B) ASM treatment alone.



As per the NICE reference case,[4] costs and benefits were discounted at an annual rate of 3.5% and a cost-effectiveness threshold of £20,000 to £30,000 per quality-adjusted life year (QALY) was used. The model had a 10-year time horizon to capture the most relevant costs and benefits for which there is evidence to populate the model.

All patients began in the "<50% seizure reduction" (no response) health state. VNS patients and ASM patients could transition between health states for the first 3-months based on data from the E03 and E05 clinical trials (Table 1), with VNS patients able to achieve a further improvement in their seizure reduction up to 24 months post-implantation, based on the relative increase in VNS responders (40% to 58%) and seizure free patients (2.5% to 6%) in the Englot et al. systematic literature review.[5] The patient response category was fixed thereafter. In patients with VNS device explantation or an inadequate response, reversal to the health-related quality of life (HRQoL) and costs of the ASM patient "no response" health state was assumed. It was assumed that the ASM patients remained in their 3-month health state for the remainder of the time horizon.

Table 1. The base-case transition state probabilities for the first 3-month cycle.

Health states	ASM	VNS+ASM
<50% seizure reduction	0.843	0.742
50-74% seizure reduction	0.138	0.166
75-99% seizure reduction	0.019	0.086
100% seizure reduction	0.000	0.007

Real-world registry implant data was used to generate Kaplan-Meier curves of explantation and battery replacement, both of which incur an additional cost.[6] Extrapolation of the curves was used to obtain explantation and battery replacement probabilities over the 10-year time horizon.

Adverse events commonly observed in VNS clinical trials, hoarseness, cough and dyspnoea, were informed by 1-, 2- and 3-year incidence rates from a long-term efficacy study.[7] Another complication of VNS implantation is surgical site infection with an observed rate of 1.3%.[8] The cost of treating infection was not modelled separately, since the all-absorptive NHS reference costs was assumed to cover the average cost of post-surgical treatment and the impact on HRQoL was considered transient and minimal.[9,10] Health state utility scores were derived from Messori et al., who used the time trade-off method.[11] All health state utilities were age- and gender-adjusted throughout the time horizon.[12] Health-state costs associated with epilepsy included hospitalizations, emergency department visits, neurologist visits, and primary care visits. Table 2 shows the annual cost per health state and the unadjusted health state utility values.

Table 2. Health state annual costs and utility values

Health state	Annual cost	Health state utility value
<50% seizure reduction	£11,863	0.66
50-74% seizure reduction	£3,926	0.79
75-99% seizure reduction	£3,322	0.91
100% seizure reduction	£285	0.96

The derived costs of VNS implantation (£21,238), replacement (£18,511) and explantation (£7,392) included the cost of consumables, procedure, training and neurologist visits for VNS interrogation and programming. The cost of pharmacotherapy was £683 per patient per cycle in both strategies.

To investigate the uncertainty around the model's key variables and assumptions, a probabilistic sensitivity analysis (PSA) and deterministic sensitivity analyses (DSA) were performed.

Results

Base-case analysis

The cost-effectiveness analysis estimated a respective incremental total cost and QALY gain of £8,430 and 0.476 for VNS + ASM versus ASM alone, per patient. The incremental cost-effectiveness ratio (ICER) was £17,711 per QALY gained, suggesting that VNS is a cost-effective treatment option in the English healthcare setting. Base-case results are given in Table 3.

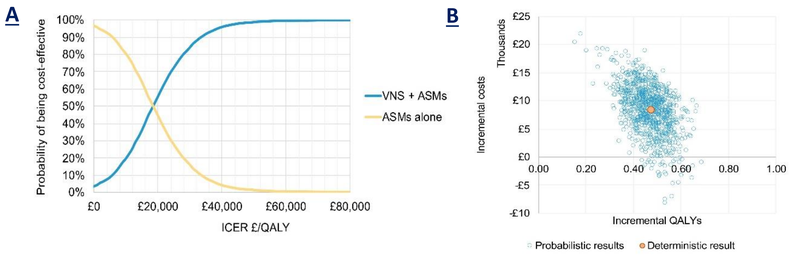
Table 3. Base-case incremental cost-effectiveness results (discounted)

Treatment	Total costs	Total life years	Total QALYs	ICER (£/QALY)
ASM	£112,011	8.387	5.642	-
VNS+ASM	£120,441	8.387	6.118	£17,711

Probabilistic sensitivity analysis

PSA results (Figure 2) determined that VNS has a 55% and 84% probability of being cost-effective at a £20,000 and £30,000 threshold, respectively.

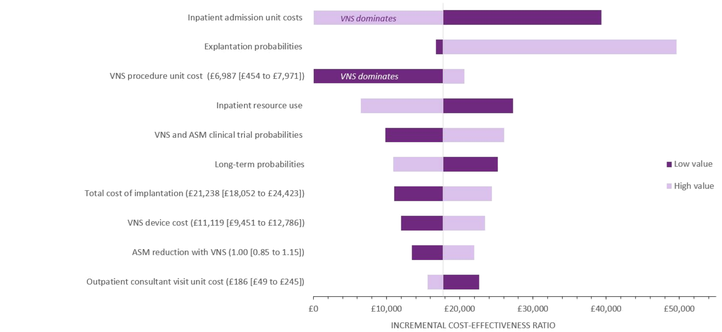
Figure 2. PSA results. A – cost-effectiveness acceptability curve. B – scatter plot.



Deterministic sensitivity analysis

The DSA varied parameter values by the uncertainty range reported from the source, or by ±15% where this was not available. The most sensitive parameters were shown to be inpatient admission unit costs, explantation probabilities, VNS procedure unit cost, inpatient resource use, and VNS and ASMs clinical trial probabilities (Figure 3). Barring extreme inputs for explantation probability and inpatient unit costs, all sensitivity analysis resulted in ICERs below the £30,000 per QALY threshold. Results were most sensitive to unit costs of inpatient care, with VNS expected to be dominant if the cost of a non-elective care admission exceeded £2,225.

Figure 3. DSA results – tornado plot of the ten most sensitive parameters.



Note that where the lower or upper bound applied to the group of inputs informing the parameter were varied simultaneously, individual values are not displayed.

Limitations

- The trials informing efficacy were not specific to VNS against ASM therapy alone (they were for VNS at "high" versus "low" stimulation). It is unclear how the sham arm efficacy estimates would compare to those from modern ASMs to treat DRE. The analysis may be conservative due to residual treatment effect of low stimulation VNS represented in the ASM strategy.
- There are conservative assumptions that seizure frequency doesn't impact mortality.
- The use of a <50% seizure reduction health state to reflect non-responder patients may not be sufficiently granular to capture the potential wide-ranging HRQoL and healthcare costs of patients who fall into this category.
- The sparse evidence of resource utilisation and costs of care specific to DRE patients in the percentage seizure reduction categories necessitated mapping of values from various sources. Conclusions of the analysis could change should future research indicate a different ratio of health care resource utilization between health states.

Conclusions

Using contemporary estimates of cost, replacement and explantation events, this model reveals that VNS adjunct to ASMs could provide a cost-effective DRE therapy in an English healthcare setting with a base-case ICER of £17,771. The conclusion is driven by a demonstrated reduction in seizure frequency with VNS, which is consequently expected to improve a patient's HRQoL and reduce downstream medical costs. Sensitivity analyses were conducted to support this argument, displaying a high probability of a cost-effective result. Further research in the relationships between seizure frequency, seizure severity, patient and carer HRQoL, and healthcare resource use should be conducted to improve future economic evaluations.

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This study was sponsored by Livanova PLC and developed by Symmetron Ltd.