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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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CR and VP developed the economic model and undertook the initial analysis and interpretation of results.
FB and JM provided advice on the conceptual model, and assisted in the provision of data that informed the model.
CR and VP drafted the manuscript, with kind medical writing assistance from Jana Tillotson. LS, RS, FB, JM and VD provided review of model structure, inputs and contributed to the interpretation of results.
All authors contributed to the critical revision and final review of the manuscript.

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**Abstract**

**Introduction:** Anti-seizure medications (ASMs) are commonly used to prevent recurring epileptic seizures, but around a third of people with epilepsy fail to achieve an adequate response. Vagus nerve stimulation (VNS) is clinically recommended for people with drug-resistant epilepsy (DRE) who are not suitable for surgery, but the cost-effectiveness of the intervention has not recently been evaluated. The study objective is to estimate costs and quality-adjusted life years (QALYs) associated with using VNS as an adjunct to ongoing ASM therapy, compared to the strategy of using only ASMs in the treatment of people with DRE, from an English National Health Service perspective.

**Methods:** A cohort state transition model was developed in Microsoft Excel® to model costs and QALYs of the VNS+ASM and ASM only strategies. Patients could transition between five health states, using a 3-month cycle length. Health states were defined by an expected percentage reduction in seizure frequency, derived from randomised control trial data. Costs included the VNS device as well as its installation, setup, and removal; ASM therapy; adverse events associated with VNS (dyspnoea, hoarseness and cough); and health-state costs associated with epilepsy including hospitalizations, emergency department visits, neurologist visits and primary care visits. A range of sensitivity analyses, including probabilistic sensitivity analysis, were run to assess the impact of parameter and structural uncertainty.
**Results:** In the base case, VNS+ASM had an estimated incremental cost-effectiveness ratio (ICER) of £17,771 per QALY gained compared to ASMs alone. The cost-effective ICER was driven by relative reductions in expected seizure frequency and the differences in health care resource use associated therewith. Sensitivity analyses found that the amount of resource use per epilepsy-related health state was a key driver of the cost component.

**Conclusions:** VNS is expected to be a cost-effective intervention in the treatment of DRE in the English National Health Service.

**Keywords:** Cost-effectiveness model; drug-resistant epilepsy; economic evaluation; epilepsy; vagus nerve stimulation; Markov model; anti-epileptic drugs

**JEL Codes:** C60; C6; C02; C31; C3; I19; I1; I
Plain Language summary

People with epilepsy are usually given anti-seizure medications (called ASMs) to help prevent their seizures from reoccurring. However, around a third of them will keep having seizures even with the medication; this is called drug-resistant epilepsy (DRE). Treatment options for DRE include, but are not limited to, surgical or therapeutic device related interventions or trying alternative ASM combinations.

In the English National Health Service (NHS), vagus nerve stimulation (VNS) therapy is recommended by the National Institute for Health and Care Excellence (NICE) for DRE patients who are still having seizures despite trying a number of different ASMs, and who cannot have brain surgery. Following NICE technical standards, we developed an economic model to test whether VNS would be a cost-effective add-on to ASM therapy. The model uses current costs for VNS therapy and takes a more nuanced approach to the longevity of the VNS device than previous research did.

Results showed that adding VNS to ASMs can be a cost-effective way to treat DRE in today’s NHS in England. VNS reduces the number of seizures, which is expected to improve patients’ quality of life and cut NHS costs that would otherwise have been needed to look after patients who had a seizure (for example, emergency visits or inpatient hospital stays). Sensitivity analyses tested aspects of uncertainty in our model. These highlighted the need to further understand the relationship between seizures, their severity and health care usage, if we want to make improved cost-effectiveness analyses about DRE in the future.
Introduction

Epilepsy is a common and serious neurological disorder, affecting up to five million new people every year, with a global prevalence of approximately 50 million [1]. People with epilepsy can suffer from frequent and recurring seizures, varying in nature and severity [2]. There is a wide range of potential impacts both on the quality of life of patients and their caregivers [3], as well as the amount of health care resources required to manage the condition [1].

The goal of epilepsy management is to reduce the frequency of seizures, and anti-seizure medications (ASMs) are the most common therapeutic intervention. ASM treatment usually starts as monotherapy and may progress to a combination of drugs if needed [4]. Approximately a third of people with epilepsy fail to achieve an adequate response to treatment with ASMs and can be described as having drug-resistant epilepsy (DRE) [5]. Prevalence of DRE varies according to region and the definition of drug resistance [6-10]. The Task Force of the International League Against Epilepsy (ILAE) Commission on Therapeutic Strategies defines DRE as a failure of adequate trials of two tolerated and appropriately chosen and used ASM schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom [5]. People with DRE require more hospitalisations and emergency department visits compared to people whose epilepsy is successfully managed with ASMs, and their mental health and quality of life are significantly poorer on average [11-13]. Depressive symptoms have been identified in over one half of people with DRE [14] and cognitive impairment is a common feature [11].

Vagus nerve stimulation (VNS) has been an important option for managing DRE for three decades, with approximately 125,000 patients across 85 countries having received the treatment since 1989 [15]. International clinical bodies recommend VNS as an effective and well-tolerated treatment for people with DRE whose options for pharmacotherapy or surgery are limited [4,16,17]. In England for example, the National Institute for Health and Care Excellence (NICE) recommends VNS as an adjunct to ASMs in treating adults, young people and children with DRE who are not suitable for resective surgery [4].
A sizable body of evidence now exists to demonstrate that VNS is clinically effective and several studies [18-20] have found it to be cost-effective owing to the reduction in seizure frequency, which consequently is expected to improve the patients’ quality of life and reduce downstream healthcare costs [21-23]. However, a contemporary analysis has not been conducted to estimate the cost-effectiveness of VNS in the English healthcare setting.

The aim of this study is to evaluate the cost-effectiveness of VNS in combination with ASM compared to ASM alone, for the treatment of people with DRE from an English NHS and personal social services (PSS) perspective, according to the standard methodology set out by NICE for health technology appraisals. To meet this aim, our objective was to develop an economic model to estimate and compare the costs and benefits (expressed as quality-adjusted life years [QALYs]) and derive an incremental cost-effectiveness ratio (ICER).
Methods

The Methods section provides a brief overview of the economic analysis. A full account of all modelling elements and considerations is provided in the Technical Supplement.

Design and population

This was a cost-utility analysis developed according to NICE’s technology appraisal guidance [24]. Costs and benefits of two DRE management strategies were estimated and compared:

1. ASM regimen as typically administered in DRE management, with no VNS;
2. VNS administered as adjunct to ASM regimen.

Health benefits were estimated as QALYs, and costs took an English NHS and PSS perspective. To take into account time preference, costs and benefits were discounted at an annual rate of 3.5%, as specified by the NICE reference case [24]. A time horizon of 10 years was used to capture the most relevant costs and benefits relating to the treatment decision for DRE for which there is evidence to populate the model. If the incremental cost-effectiveness ratio (ICER) is below the acceptable threshold, the intervention of interest can be considered cost effective. To assess cost effectiveness of VNS in our analysis, the NICE cost-effectiveness threshold range of £20,000 per QALY to £30,000 per QALY was used [24]. The likelihood of cost-effectiveness given alternative thresholds was also calculated and is presented as a cost-effectiveness acceptability curve.

Primary data on the efficacy of VNS were sourced from two randomised controlled trials (RCTs) (named E03 and E05) evaluating the efficacy of high versus low stimulation VNS therapy given adjunctively to ASM [25,26]. For the purposes of modelling, adjunctive low stimulation therapy was assumed to be equivalent to ASM therapy only. These two RCTs also informed population characteristics used for the model cohort, as summarized in Table 1. Both trials had a small proportion of children participating; these were included and adjusted for accordingly in the costing, but the purpose of this analysis is primarily to model costs and benefits in the adult population, and not to model in detail the management of DRE in children.
Model structure

We developed a cohort state transition model in MS Excel (version 2016). In line with previous cost-effectiveness analyses in this therapy area [30,31], health states were defined by percentage reductions in seizure frequency achieved from baseline:

- 100% reduction (seizure-free);
- 75-99% reduction (responder);
- 50-74% reduction (responder);
- less than 50% reduction (no response).

Death was also modelled. Cycle length was set to 3 months, to correspond with the study durations of trials E03 and E05. Model structure is shown in Figure 1 and Figure 2.

By default, all patients started in the ‘no response’ health state. VNS patients were able to transition between health states any time up to 24 months post-implantation, after which their health state was assumed to remain fixed (subject to death or discontinuation). ASM patients could move between health states in the first 3-month cycle, and thereafter their response category was assumed to remain static. Costs (other than the initial VNS implantation) and outcomes were half-cycle corrected.

VNS patients could discontinue treatment due to explantation at any point or due to inadequate response at 24 months, at which point the device was assumed to be deactivated. In both cases, patients would revert to the health-related quality of life (HRQoL) and costs of ASM patients in the ‘no response’ health state. Deactivation does not require an invasive procedure or additional cost to a routine care appointment, and is essentially a continuance of VNS implantation without associated benefits or risks of VNS treatment (with the exception of explanation to remove the device later if required).

The likelihood of explantation and battery replacement were modelled over time using real-world data and fitted parametric curves (see Discontinuation).

Figure 1. Model structure - treatment with VNS and ASM

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**Clinical evidence inputs**

**Format**

Input parameters were calculated as means. Upper and lower limits for the deterministic sensitivity analysis (DSA) were derived from reported statistics in the source material unless otherwise indicated in the tables.

**Efficacy and health state transitions**

For VNS patients, individual level patient data (IPD) from the E03 and E05 [27] studies were used to inform effectiveness estimates (expressed as a relative percentage improvement in seizure frequency between VNS and control arm) over the first three months of the model. Longer-term effectiveness of VNS was informed by the relative increase in ‘responder’ and ‘seizure free’ patients from a systematic review of long-term outcomes in VNS-treated patients, carried out by Englot et al (2016) [32]. The systematic review found that patients’ response to VNS, and movement toward freedom from seizures, continued over a 2-year period after initiation of VNS and the response rate was sustained thereafter until at least 4 years [32]. This trend was further supported by a real-world registry analysis also conducted by Englot et al. in their 2016 publication [32], as well as an open-label, long-term efficacy study of VNS patients enrolled in the E01-E05 trials conducted by Morris et al. [16].

For the DRE patient cohort treated with ASMs only, their prior established non-response to epilepsy medication could lead one to assume that overall, their therapy will yield a reduced response over time. However, because there is limited evidence to model the longer-term response for DRE ASM patients, our model took a conservative assumption that ASM patients would maintain the same level of response and seizure frequency observed in the “low stimulation” arm patients at the end of the E03 and
E05 trial period at 3 months. Applied to the model, this meant that despite having drug resistance, around 16% of ASM patients remained in “responder” health states throughout the model time horizon.

Transition probabilities developed based on clinical evidence are summarised in Table 2. Sensitivity analyses were undertaken to test the impact of a reduced treatment effect of VNS in the longer term as well as an increased return to the “no response” state for ASM patients.

Adverse events
Only adverse events associated with VNS were considered in the model. Three adverse events identified as commonly observed in VNS clinical trials [33] were included as shown in Table 3. Per-cycle adverse event probability was informed by 1, 2, and 3+ year incidence rates reported in Morris et al. [33]. Other events, such as cognitive effects associated with ASMs [34], were not modelled as the base case assumed both cohorts, whether on VNS or not, would continue to receive the same stable ASM regimens throughout the time horizon.

The most common complication of VNS implantation is surgical site infection [35]. The observed wound infection rate post implantation is 1.3% [36]. The cost of treating infection was not modelled separately, since the NHS reference cost used for VNS-related procedures covers the potential costs of recovery, infection management and other related issues. Surgical site infection was considered to have a transient, and therefore minimal, impact on HRQoL across the time horizon.

Discontinuation of therapy or replacement due to battery depletion
Patients receiving VNS could discontinue treatment due to non-response to therapy (leading to the deactivation of the device) or if their device had to be explanted, with the latter involving an additional cost of an explantation procedure. Replacement of the VNS device due to battery depletion is associated with a respective cost, however, patients continued to benefit from VNS in terms of their health status.

Real-world registered implant data from the United States (US), detailing the use of VNS (Aspire SR 106) in 24,686 patients for up to 7 years, were used to generate
Kaplan-Meier data regarding explanation and replacement probabilities (data on file, provided by LivaNova) [15].

A range of curve functions based on these data was tested and assessed for goodness of fit, with generalised gamma and Gompertz functions selected for explantation and replacement respectively (see Figure 3 and Figure 4). Full details of the extrapolation and goodness-of-fit assessment statistics are provided in the Technical Supplement. To test the lower and upper bounds of uncertainty in deterministic sensitivity analysis, the lower and upper 95% confidence interval for the coefficients feeding into the extrapolation were used.

**Figure 3. Extrapolation function - time to VNS device explantation**

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**Figure 4. Extrapolation function - time to VNS device replacement**

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**Drug reductions**

Observational studies suggest that successful VNS treatment can alleviate the need for ASM use in the long term [37,38]. This potential benefit was not modelled in the base case, since the E03 and E05 trial protocols did not stipulate ASM dose reductions. However, a study by Tatum et al. [37] observed 48% of VNS patients had a reduction in ASM dosage compared to 10% in the control group, with a mean change in ASM use per VNS patient of -0.43 (reflecting approximately a 15% reduction in use from baseline). To explore the impact on the ICER, a threshold analysis was designed which modelled a range of ASM dose reduction levels for a selection of typical ASM regimens.

**Health related quality of life**

A utility score for each health state was obtained using data from a prospective study of 81 patients by Messori et al. [22], which estimated time trade-off utilities for a set of
seizure frequency categories. These categories, which reflected absolute numbers of seizures, could be mapped with reasonable similarity onto the percentage seizure reduction categories in E03 and E05. Messori et al. was selected as the evidence source over other studies [23,39], because it used the NICE-preferred method for estimating utilities and had a distribution of seizure frequencies which most closely resembled E03 and E05 study populations.

To derive utilities for each health state, we calculated the relative difference between utilities for lower response states and the ‘seizure free’ health state (which was assumed initially to be equal to the English general population [29]). We then applied these relative differences to a baseline population value (0.92), which had been adjusted for the mean age and gender mix of the model population per the Ara and Brazier method [29]. The resulting utility values were used for each health state. Utility values used to derive health state utilities are shown in Table 4. The baseline value was adjusted for cohort mean age at each cycle, meaning all health state utilities remained age- and gender-adjusted throughout the time horizon.

The three types of VNS adverse events were modelled to have disutility, estimates of which were obtained from two published studies as shown in Table 5. Although the studies captured disutility associated with dyspnoea, cough and hoarseness, they were not carried out in DRE patient populations.

Costs and resource use

Health state costs
Healthcare resource unit costs, summarized in Table 6, were obtained from publicly available sources, in line with NICE health technology assessment methodology. General practitioner costs were taken from the latest Personal Social Services Research Unit Costs of Health and Social Care report [42]. Secondary care costs for hospital admissions, neurologist visits or VNS procedures were sourced using the most recent listing of NHS reference costs at the time of writing [43]. Because costs for people with DRE were not available, it should be noted that the costs for hospital admissions were sourced for people with nerve disorders, epilepsy or head injury, with the derived unit cost weighted for the associated activity by comorbidity score. In the sensitivity
analysis, the cost of inpatient care is varied in line with level of expected comorbidity (more detail can be found below and within the Technical Supplement).

**Health care resource assumptions**

The rate at which the above healthcare resources were used in each health state was sourced from available literature and summarised as annual values in Table 7. These frequencies were multiplied by unit costs to give annual costs as shown in Table 8.

Resource use reported for VNS patients in an English setting 3 years post-implantation was used for the 50-74% health state [34]. No data on the resource use of DRE patients who achieved a 75-99% reduction in seizures were identified. It was assumed that the relative decrease of 15% in the mean seizure frequency of patients achieving a 50-74% and 75-99% seizure reduction in the E03 and E05 clinical trials would correspond to an equivalent relative decrease in resource use between these health states. In the absence of a UK study, the lower bounds of the incidence rate ratios of “well-controlled” versus “uncontrolled” epilepsy in the US [21] were applied to the 75-99% health state to derive resource use for the <50% health state. English guidelines recommend that people with epilepsy should have a regular structured review, which may be carried out by a specialist depending on the person’s wishes, circumstances and epilepsy [4]. The guidance also recommends specialist referral for management of refractory epilepsy [4]. On this basis, it was assumed a typical patient with DRE would have 1.5 annual outpatient visits if they were seizure free. It was also assumed that 10% of the annual outpatient visits for patients in any health state would require an additional GP visit, in addition to an assumed 0.01 probability of a GP visit per seizure. This approach to primary care resource estimation is in line with a previous cost-utility study in refractory epilepsy [31].

**Anti-seizure medication costs**

No direct evidence on the schedules of ASMs administered to DRE patients was identified for the English context, with important epilepsy studies not reporting on the regimen for DRE patients specifically [44-46]. Studies E03 and E05 did not capture specific ASM prescription details; they are also several decades old meaning they are neither sufficiently detailed nor current to inform a contemporary analysis.
As an alternative, a weighted average quarterly cost of £683 per patient, based on an assumed basket of three ASMs, was applied in both groups. The percentage mix of specific drugs within this schedule was informed by the NHS Prescription Cost Analysis (PCA) database [47]; unit costs and typical doses were sourced from the National Drug Tariff and the British National Formulary (BNF) [48]. The derivation of the ASM cost is provided in the Technical Supplement.

The combined impact of ASM dose reduction for VNS patients, together with using specific, alternative regimens of multiple ASMs, was explored in a scenario analysis.

**VNS costs – implantation, explantation and battery replacement**

An overview of the values used to estimate the cost of VNS implantation, as well as its explantation and replacement where applicable, is given in Table 9. The costs of VNS implantation, explantation and replacement includes additional neurologist visits for VNS interrogation and programming.

**Adverse event costs**

Table 10 details the expected resource use and associated cost for a patient experiencing one adverse event over the course of one year. The mean cost per cycle was estimated and applied proportionally to the percentage of the cohort experiencing the event in any given three-month cycle.

**Sensitivity and scenario analyses**

**Deterministic sensitivity analysis**

This was undertaken to identify the key drivers of model outcomes by varying single parameters, or groups thereof as appropriate by a plausible minimum and maximum range reported from the source, or where this was unavailable by ±15%, keeping all other inputs constant.

**PSA**

Parameter uncertainty was assessed by probabilistic sensitivity analysis (PSA), using 5,000 simulations and the likelihood of being cost-effectiveness at various thresholds evaluated. The parameter distributions used in PSA are provided in the Technical Supplement.
Other sensitivity analyses
A set of threshold and scenario analyses was designed to test the model’s sensitivity to
the following concepts:

- mapping healthcare resource use to health states;
- assumptions regarding longer-term treatment effect;
- reducing ASM use whilst on VNS, testing a range of alternative ASM regimens;
- expected inpatient and elective cost burden for a DRE patient, with various
  levels of comorbidity and complexity.

Scenario analyses and their results are reported in detail in the Technical Supplement.
Results

Base case

The cost-effectiveness analysis estimated an incremental total cost of £8,430 and an incremental QALY gain of 0.476 for VNS + ASM versus ASM alone. The ICER was £17,711 per QALY gained, suggesting that VNS is a cost-effective treatment option in the English healthcare setting. Detailed results are shown in Table 11.

Sensitivity analysis

Of all the deterministic sensitivity analyses undertaken (see Table 12 and Figure 5), only the input of extreme values for explantation probability and inpatient unit costs resulted in a cost-ineffective ICER relative to NICE thresholds of £20,000 to £30,000 per QALY gained.

The ICER remained under the £30,000 threshold in all sensitivity analyses that tested a 15 percent variation in the overall costs of implant, replacement and explant, respectively. Including costs for additional follow up neurologist visits for programming or increased cost of treatment of adverse events is not expected to change conclusions of the analysis.

Figure 5. Tornado diagram

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Abbreviations: A&E, hospital accident & emergency department; ASM, anti-seizure medication; GP, general practitioner; NMB, net monetary benefit; QALY, quality adjusted life year; SMR, standardized mortality ratio; TRAE, treatment-related adverse event; VNS, vagus nerve stimulation. Notes: Where a parameter sensitivity analysis involved change to a single value, lower and upper bound values are shown on the diagram; * applied for the cost of the procedure related aspect of implant and replacement; ¥ lower or upper bound applied to the group of inputs informing the parameter simultaneously.

Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis, VNS was dominant (more effective and less costly) in 3.48% of the 5000 iterations, with a probabilistic incremental net monetary benefit of £843 (95% CI: -£8,415 to £11,508). VNS was likely to be cost-effective at the
£20,000 threshold in 55% of iterations and at the £30,000 threshold in 84% of iterations. PSA scatterplot and cost-effectiveness acceptability curves are shown in Figure 6.

**Figure 6. Probabilistic sensitivity analysis - scatter plot and cost-effectiveness acceptability curve**

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Scenario analyses

**Mapping healthcare resource use to health states**
Because of the uncertainty associated with mapping healthcare resource use to seizure reduction health states, a set of scenario analyses, provided in the Technical Supplement, was run to test the various assumptions required in this mapping. It was apparent that the cost-effectiveness results are sensitive to different healthcare resource use assumptions. If future research indicates a different ratio of health care resource utilisation between health states, then conclusions of the analysis could change.

**Assumptions regarding longer-term treatment effect**
A range of analyses which varied either the amount or duration of VNS effect, or the duration of patient response to treatment, showed that the ICER was robust to a wide range of uncertainty around its real-world and longer-term effectiveness (inclusive of a reduction in treatment effect) remaining below £30,000/QALY in all tested scenarios.

**Reducing ASM use whilst on VNS, testing alternative ASM regimens**
This analysis illustrated that if VNS patients have a reduction in their ASM consumption, the cost-effectiveness of VNS improves. For example, if the reduction in ASM use reported by Tatum et al. [37] is modelled using the base-case bundle of ASMs, the ICER reduces to £13,364.

In the base case, the approximated cost of a bundle of ASMs is inconsequential to the incremental results because VNS was not assumed to affect ASM consumption. However, to obtain a more detailed overview of scenarios where VNS patients are able to reduce their ASM use, we undertook analyses testing a series of costs of ASM combinations believed to be typically trialled by people with DRE, alongside
hypothetical percentage reductions in ASM use. The higher the cost of the ASM bundle which the patient starts with, the more sensitive the percentage reduction in ASM use becomes and the more cost-effective VNS, as shown in the Technical Supplement.

**Expected inpatient and elective cost burden for a DRE patient**

As the cost of inpatient care associated with health states was found to be a key driver in the cost-effectiveness analysis, a further two-way sensitivity analysis was conducted whereby costs derived for groups of increasing comorbidity (defined by the HRG complications and comorbidity [CC] score) were examined. For example, VNS was expected to be dominant (more effective and cost saving) if the costs associated with a CC score above 9 were applied for hospitalisation. Only when costs were at the minimum value for non-elective care (i.e. for a short stay of a patient with a CC score of 0-2) was VNS found to be not cost-effective (full table in Technical Supplement).

**The cost associated with the procedure of implant, explant and replacement**

The base-case analysis used the combined cost for the VNS device and the all-absorptive NHS reference cost to estimate the surgical costs of the procedure involved. However, as the scenario analysis revealed, substituting the NHS reference cost of the procedure with that of the NHS tariff (which should represent catch-all cost items that trusts can charge for VNS procedures) resulted in a markedly lower ICER of £5,766.
Discussion

Overview and context

This economic model provides a comprehensive case, that uses contemporary estimates of cost, replacement and explantation events, for the cost-effectiveness of VNS in the treatment of DRE in the English NHS, with a base-case ICER of £17,771 per QALY. A few older analyses exist [19,20], but they do not use current costs, guidelines, or research and none utilised real-world evidence on VNS explantation or replacement.

The main benefit of VNS in DRE management is that it reduces seizure frequency and the often-costly healthcare interventions which DRE requires. For example, the reduction in inpatient, outpatient and emergency care costs associated with improved control of epilepsy [21, 34] is expected to offset the costs of the VNS intervention sufficiently that VNS is considered a cost-effective treatment. Furthermore, there is a potential for some VNS-treated patients to be able to reduce their burden of ASM regimens [37] and rescue medications, which could not only save costs of the medication but also lead to an alleviation of medication side effects [37].

The conclusion of cost-effectiveness, utilising the NICE threshold range, was robust to nearly all sensitivity analyses and only generated cost-ineffective ICERs in a minority of scenarios. Firstly, a cost-ineffective ICER was generated where health care unit cost for hospitalisation was assumed to be unrealistically low when applied on a cohort basis (i.e. assuming that all DRE patients have the lowest patient complexity and comorbidity score and shortest reported length of stay, even though the evidence suggests a heterogeneous case mix inclusive of high-comorbidity patients [11,43]). Secondly, a cost-ineffective ICER was generated when upper confidence limits for the extrapolation curve coefficients were used and resulted in unrealistic estimates for the probability of needing explantation – in this extreme scenario, an assumed 22% of patients needed explantation within the first cycle and 27% needed explantation by the end of the time horizon. However, the Kaplan Meier data at 7.14 years (last known explant) suggest a probability of explantation (for any cause) of only 2% at this time point (see Figure 3). Finally, varying assumptions in the estimation of health state
resource use had potential to both increase and decrease the ICER. Further research regarding resource use in relation to seizure frequency would be of benefit in modelling this aspect more robustly.

The choice of extrapolation function for the long-term probability of VNS device replacement may have underestimated the longevity of the VNS device when compared to what is observed in real clinical practice (see Figure 3)[15]. However, in this study, time to replacement did not feature as a sensitive parameter because the cost of expected replacement was incurred within the time horizon and only the timing of the cost changed. This differs from the impact of explant, whereafter patients returned to a ‘no response’ health state, experiencing no treatment benefit at all for the rest of the time horizon. Further, forcing deactivation at 24 months due to lack of response was a simplification made for purposes of this cohort model, whereas it is suspected in practice that individual non-responding patients would continue with an activated device beyond this point with potential to respond.

Our model results are consistent with existing research from the UK. Forbes et al. (2003) reported an ICER of £28,849 per QALY for a time horizon of 5 years and a Scottish perspective [20]. A later update by Forbes et al. in 2008 using more recent data on device longevity and estimates of efficacy led to an ICER of £4,423 per QALY [19]. In contrast, we estimate the ICER to be in between the previously published estimates, noting that our study applied a more contemporary (and higher) cost for the VNS intervention and used real-world evidence to estimate rates of VNS explanation and replacement. Camp et al. (2015) found in an English setting that healthcare resource costs, in general, decreased over the longer term after VNS was implanted [34].

The finding that health care expenditure reduces post VNS is also supported by international studies. A Belgian cost-consequences analysis reported that mean annual direct medical costs per patient reduced from US$8,830 to US$4,215 [49]; while a Danish study [50] found a statistically significant cost reduction for epilepsy-related outpatient services, inpatient admission and prescription medicine. A small Polish study reported that direct medical costs continued to reduce after VNS (EUR 53,840 versus EUR 43,120 for first and second year follow up, respectively)[51]. A US
retrospective 4-year analysis suggested statistically significant reductions in both health care utilization and time spent on health-related activities [53]. Other economic analyses from the US report expected net cost savings with VNS 1.5 to 1.7 years post VNS due to reduced resource use expenditure following the VNS procedure [52,53]. The complete offset of the cost of the VNS therapy in the US may be partially driven by the difference in resource use between uncontrolled and controlled epilepsy and high unit costs of care. The greater the difference between the costs of managing controlled versus uncontrolled epilepsy, the more cost-effective (or in the case of the US, cost saving) VNS is expected to be.

The cost-effectiveness of VNS therapy has also been evaluated in the treatment of children with DRE from a Dutch [55,56], Jordanian [18] and US [57] perspective. Although findings of such studies have limited generalisability to our English and mostly adult population of interest, the comparison between studies from the developed and developing countries suggests that a driver of downstream cost-savings is the access to and use of high-cost health care (which may be avoided with enhanced seizure control). This supports our own observation that the higher the relative inpatient care cost burden associated with uncontrolled epilepsy, the more cost-effective VNS is expected to be. It may be reasonable to hypothesize, therefore, that VNS would be of value for specific patient groups that would otherwise have seizures with a high-cost burden if hospitalised.

In summary, international evidence of cost reduction, combined with the expected reduction in seizure frequency and, by implication, improved HRQoL [22,23,39,58] supports the expectation that VNS is a cost-effective intervention.

**Strengths and limitations**

The strengths of the model include its use of bespoke analyses from IPD of 310 trial patients to inform effectiveness estimates, and its use of extrapolation functions based on large-scale, long-term registry data to estimate device longevity.

Limitations include the use of health states defined by a percentage reduction in seizure frequency, rather than absolute frequencies of seizures. This approach, whilst consistent with trials E03 and E05, as well as other published economic evaluations
created challenges when mapping costs and utilities from various sources in the literature. In particular, the mapping from different sources to inform health state resource use introduced uncertainty into conclusions. Despite our rigorous and cautious approach to mapping, it remains unclear exactly how closely the true distribution of seizure frequency in the model population aligns with those of studies in the literature which we used for our estimates of healthcare resource use and utilities.

The analysis utilised data specific to DRE patients wherever possible, but there is limited evidence about the resource utilisation and unit costs of care for people with DRE specifically. For the VNS cohort, resource estimates were primarily informed by all-cause hospital admissions (as reported by Camp et al.[34]) rather than admissions specifically linked to epilepsy. This was done to avoid missing hospital resource use which is not coded with a primary diagnosis of epilepsy but is nonetheless likely to be linked to poor seizure control. In this regard, it is notable that Camp et al. reported a decrease in resource use after VNS therapy, both for admissions coded with a primary diagnosis of epilepsy and for all patient admissions. The study did not report specifically on more expensive “intensive care” stays, and as such we may have underestimated cost of hospitalisation if VNS has a treatment effect on this parameter. Sensitivity analysis suggests that the greater the cost of the inpatient stay, the more cost-effective VNS is likely to be; however, granular cost and resource data specific to the DRE population would be required to fully understand the impact of uncertainty introduced by our resource and cost estimation.

More broadly, the resource use component did not account for the cost of social care, despite this potentially being substantial given the needs of people with DRE and their carers when living and managing their condition in the community.

A further limitation is that the trials informing efficacy did not compare VNS therapy against ASM therapy only. The E03 and E05 studies compared VNS at ‘high stimulation’ settings to a presumed sub-therapeutic ‘low stimulation’ regimen. ASMs were given in both arms. The observed efficacy of the ‘low stimulation’ arms from E03 and E05 informed the estimated efficacy of the modelled ‘ASMs only’ strategy. It is possible
that any residual benefit of ‘low stimulation’ led to the efficacy of the modelled strategy of ASMs only being overestimated. Furthermore, the original trials of VNS used are several decades old. Therapeutic advances in VNS treatment (e.g. implant technology, diagnostics, imaging, surgical procedures) since the time of the trials could mean that the model omits potential benefits of current VNS therapy.

Advances in ASM therapy could also be expected to reduce seizure burden when used in isolation or with VNS adjunctively. However, a relatively contemporary UK observational study concluded that that seizure freedom rates have remained virtually unchanged for the past two decades despite the introduction of new therapies [44]. Although the study notes a higher rate of seizure freedom than suggested by E03 and E05 trials, the incremental benefit of VNS as an adjunct to modern ASMs compared with the older ASMs remains unclear, due to the lack of comparative studies. Further research would be required to understand the impact of including newer therapies.

Finally, the analysis conservatively assumed that seizure frequency would not impact on mortality and no change to cost or HRQoL would be expected if a patient experienced less than a 50% reduction in seizures. The omission of a mortality relationship may be important since sudden unexpected death in epilepsy (SUDEP) has been estimated to account for 38% of deaths in people with epilepsy [63]. There are also potentially further incremental gains in HRQoL and costs between DRE patients who achieve some form of response to therapy versus those who do not; this may not be adequately captured by the five health state model framework. For example, even a low percentage reduction in the frequency of severely disabling seizures could substantially reduce health care cost burden and improve HRQoL.

**Conclusions**

VNS is considered to be a cost-effective intervention as an adjunct to ASMs in people with DRE who are not considered suitable for surgery. The conclusion is driven by a demonstrated reduction in seizure frequency with VNS [25,26], which is consequently expected to improve a patient’s health-related quality of life and reduce downstream medical costs. A wide range of potential scenarios were explored which indicated that
VNS was cost-effective using a £20,000 to £30,000 cost-effectiveness threshold, despite the base case holding several conservative assumptions. Future economic evaluations would benefit from further research in the relationships between seizure frequency, seizure severity, patient and carer HRQoL and, most importantly, healthcare resource use.

References

1. World Health Organisation. Health Topics: Epilepsy. 2019. Available at: https://www.who.int/health-topics/epilepsy
2. Beghi E. The Epidemiology of Epilepsy. Neuroepidemiology. 2020;54(2):185-191
3. Karakis I, Cole AJ, Montouris GD, et al. Caregiver burden in epilepsy: determinants and impact. Epilepsy Res Treat. 2014;2014:808421.
4. National Institute for Health and Care Excellence. Epilepsies: diagnosis and management (CG137). 2012. Available at: https://www.nice.org.uk/guidance/cg137/chapter/1-Guidance#vagus-nerve-stimulation-vns
5. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010 Jun;51(6):1069-77.
6. Hauser WA, Beghi E. First seizure definitions and worldwide incidence and mortality. Epilepsia. 2008;49 Suppl 1:8-12.
7. Meeraus WH, Petersen I, Chin RF, et al. Childhood epilepsy recorded in primary care in the UK. Arch Dis Child. 2013 Mar;98(3):195-202.
8. Mohanraj R, Brodie MJ. Diagnosing refractory epilepsy: response to sequential treatment schedules. European Journal of Neurology. 2006;13:277-282.
9. Neligan A, Bell GS, Johnson AL, et al. The long-term risk of premature mortality in people with epilepsy. Brain. 2011 Feb;134(Pt 2):388-95.
10. Platt M, Sperling MR. A comparison of surgical and medical costs for refractory epilepsy. Epilepsia. 2002;43:25-31.

11. Dalic L, Cook MJ. Managing drug-resistant epilepsy: challenges and solutions. Neuropsychiatr Dis Treat. 2016;12:2605-2616.

12. Strzelczyk A, Griebel C, Lux W, et al. The Burden of Severely Drug-Refractory Epilepsy: A Comparative Longitudinal Evaluation of Mortality, Morbidity, Resource Use, and Cost Using German Health Insurance Data. Front Neurol. 2017;8:712.

13. Villanueva V, Girón JM, Martín J, et al. Quality of life and economic impact of refractory epilepsy in Spain: The ESPERA study. Neurología (English Edition). 2013;28(4):195-204.

14. Garcia ME, Garcia-Morales I, Gil-Nagel A. Prevalence of depressive symptoms and their impact on quality of life in patients with drug-resistant focal epilepsy (IMDYVA study).

15. LivaNova. Data on file, Personal Communications. 2021.

16. Morris GL, Gloss D, Buchhalter J, et al. Evidence-based guideline update: Vagus nerve stimulation for the treatment of epilepsy. Epilepsy Currents. 2013;13:297-303.

17. Shaw B KV, Robalino S, et al. Vagal Nerve Stimulation for Epilepsy and Depression: Final Evidence Report. Center for Evidence-based Policy, Oregon Health & Science University, 2020. Available at: https://www.hca.wa.gov/assets/program/vns-final-rpt-complete-20200520.pdf

18. Aburahma SK, Alzoubi FQ, Hammouri HM, et al. Vagus nerve stimulation therapy in a developing country: a long term follow up study and cost utility analysis. Seizure. 2015 Feb;25:167-72.

19. Forbes R. Cost-utility of vagus nerve stimulation (VNS) therapy for medically refractory epilepsy--an update. Seizure. 2008 Jun;17(4):387-88.

20. Forbes RB, Macdonald S, Eljamel SAM, et al. Cost-utility analysis of vagus nerve stimulators for adults with medically refractory epilepsy. Seizure. 2003;12(5):249-256.
21. Manjunath R, Paradis PE, Parisé H, et al. Burden of uncontrolled epilepsy in patients requiring an emergency room visit or hospitalisation. Neurology. 2012;79:1908-1915.

22. Messori A, Trippoli S, Becagli P, et al. Adjunctive lamotrigine therapy in patients with refractory seizures: a lifetime cost-utility analysis. Eur J Clin Pharmacol. 1998;53:421-427.

23. Mulhern B, Pink J, Rowen D, et al. Comparing Generic and Condition-Specific Preference-Based Measures in Epilepsy: EQ-5D-3L and NEWQOL-6D. Value Health. 2017 Apr;20(4):687-693.

24. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal. 2013. Available at: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781

25. Handforth A, DeGiorgio CM, Schachter SC, et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology. 1998;51:48-55.

26. The Vagus Nerve Stimulation Study Group. A randomized controller trial of chronic vague nerve stimulation for treatment of medically intractable seizures. Neurology. 1995;45:224-230.

27. LivaNova. Patient level seizure data for randomised controlled trials E03 (1995) and E05 (1998). Data provided by LivaNova PLC on 10 September 2020. 2020.

28. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health. 2010 Aug;13(5):509-18.

29. Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. Value Health. 2011 Jun;14(4):539-45.

30. Bolin K, Berggren F, Forsgren L. Lacosamide as treatment of epileptic seizures - cost utility results for Sweden. Acta Neurol Scand. 2010 Jun;121(6):406-12.

31. Kristian B, Wachtmeister K, Stefan F, et al. Retigabine as add-on treatment of refractory epilepsy – a cost-utility study in a Swedish setting. Acta Neurologica Scandinavica. 2013;127(6):419-426.
32. Englot DJ, Rolston JD, Wright CW, et al. Rates and Predictors of Seizure Freedom With Vagus Nerve Stimulation for Intractable Epilepsy. Neurosurgery. 2016 Sep;79(3):345-53.

33. Morris GL, 3rd, Mueller WM. Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. The Vagus Nerve Stimulation Study Group E01-E05. Neurology. 1999 Nov 10;53(8):1731-5.

34. Camp C, Smithson WH, Bunker MT, et al. Impact of vague nerve stimulation on secondary care burden in children and adults with epilepsy: Review of routinely collected hospital data in England. Epilepsy Behav. 2015;52:68-73.

35. Horowitz G, Amit M, Fried I, et al. Vagal nerve stimulation for refractory epilepsy: the surgical procedure and complications in 100 implantations by a single medical center. Eur Arch Otorhinolaryngol. 2013 Jan;270(1):355-8.

36. Selner AN, Rosinski CL, Chiu RG, et al. Vagal Nerve Stimulation for Epilepsy in Adults: A Database Risk Analysis and Review of the Literature. World Neurosurg. 2019 Jan;121:e947-e953.

37. Tatum WO, Johnson KD, Goff S, et al. Vagus nerve stimulation and drug reduction. Neurology. 2001;56:561-563.

38. Vale FL, Ahmadian A, Youssef AS, et al. Long-term outcome of vagus nerve stimulation therapy after failed epilepsy surgery. Seizure. 2011 Apr;20(3):244-8.

39. Selai CE, Trimble MR, Price MJ, et al. Evaluation of health status in epilepsy using the EQ-5D questionnaire: a prospective, observational, 6-month study of adjunctive therapy with anti-epileptic drugs. Curr Med Res Opin. 2005 May;21(5):733-9.

40. Doyle S, Lloyd A, Walker M. Health state utility scores in advanced non-small cell lung cancer. Lung Cancer. 2008 Dec;62(3):374-80.

41. Swan IRC, Guy FH, Akeroyd MA. Health-related quality of life before and after management in adults referred to otolaryngology: a prospective national study. Clinical Otolaryngology. 2011;37.

42. Curtis KA, Burns A. Unit costs of health & social care 2019. 2019. Available at:

43. NHS. National Cost Collection for the NHS: 2018/19 National Cost Collection data 2020 [29/09/2020]. 2020. Available at: https://www.england.nhs.uk/national-cost-collection/#ncc1819
44. Chen Z, Brodie MJ, Liew D, et al. Treatment Outcomes in Patients With Newly Diagnosed Epilepsy Treated With Established and New Antiepileptic Drugs: A 30-Year Longitudinal Cohort Study. JAMA Neurology. 2018;75(3):279-286.

45. Marson A, Burnside G, Appleton R, et al. The SANAD II study of the effectiveness and cost-effectiveness of valproate versus levetiracetam for newly diagnosed generalised and unclassifiable epilepsy: an open-label, non-inferiority, multicentre, phase 4, randomised controlled trial. The Lancet. 2021;397(10282):1375 - 1386.

46. Marson A, Burnside G, Appleton R, et al. The SANAD II study of the effectiveness and cost-effectiveness of levetiracetam, zonisamide, or lamotrigine for newly diagnosed focal epilepsy: an open-label, non-inferiority, multicentre, phase 4, randomised controlled trial. The Lancet. 2021;397(10282):1363 - 1374.

47. NHS Business Services Authority. Prescription Cost Analysis - England, January 2020 [PAS] 2020. Available from: https://www.nhsbsa.nhs.uk/sites/default/files/2020-04/PCA%20Jan20.xlsx

48. British Medical Association and Royal Pharmaceutical Society of Great Britain. UK British National Formulary. 2020. Available at: https://bnf.nice.org.uk/

49. Boon P, D’Have MD, Van Wallghem P, et al. Direct Medical Costs of Refractory Epilepsy Incurred by Three Different Treatment Modalities: A Prospective Assessment. Epilepsia. 2002;43:96-102.

50. Jennum P, Sabers A, Christensen J, et al. Socioeconomic evaluation of vagus stimulation: A controlled national study. Seizure. 2016 Nov;42:15-19.

51. Kopciuch D, Barciszewska AM, Flicinski J, et al. Economic and clinical evaluation of vagus nerve stimulation Therapy. Acta Neurol Scand. 2019 Oct;140(4):244-251.

52. Helmers SL, Duh MS, Guerin A, et al. Clinical and economic impact of vagus nerve stimulation therapy in patients with drug-resistant epilepsy. Epilepsy Behav. 2011 Oct;22(2):370-5.

53. Purser MF, Mladsi DM, Beckman A, et al. Expected Budget Impact and Health Outcomes of Expanded Use of Vagus Nerve Stimulation Therapy for Drug-Resistant Epilepsy. Adv Ther. 2018 Oct;35(10):1686-1696.
54. Bernstein AL, Hess T. Vagus nerve stimulation therapy for pharmacoresistant epilepsy: effect on health care utilization. Epilepsy Behav. 2007 Feb;10(1):134-7.

55. Majoie MH, Berfelo MW, Aldenkamp AP, et al. Vagus nerve stimulation in children with therapy resistant epilepsy diagnosed as Lennox-Gastaut syndrome. Journal of Clinical Neurophysiology. 2001;18:419-428.

56. de Kinderen RJ, Postulart D, Aldenkamp AP, et al. Cost-effectiveness of the ketogenic diet and vagus nerve stimulation for the treatment of children with intractable epilepsy. Epilepsy Res. 2015 Feb;110:119-31.

57. Helmers SL, Duh MS, Guerin A, et al. Clinical outcomes, quality of life, and costs associated with implantation of vagus nerve stimulation therapy in pediatric patients with drug-resistant epilepsy. Eur J Paediatr Neurol. 2012 Sep;16(5):449-58.

58. Dodrill CB, Morris GL. Effects of Vagal Nerve Stimulation on Cognition and Quality of Life in Epilepsy. Epilepsy Behav. 2001 Feb;2(1):46-53.

59. Craig D, Rice S, Paton F, et al. Retigabine for the Adjunctive Treatment of Adults with Partial-Onset Seizures in Epilepsy with and without Secondary Generalization. PharmacoEconomics. 2013 2013/02/01;31(2):101-110.

60. Hawkins N, Epstein D, Drummond M, et al. Assessing the cost-effectiveness of new pharmaceuticals in epilepsy in adults: the results of a probabilistic decision model. Med Decis Making. 2005 Sep-Oct;25(5):493-510.

61. Simoens S, De Naeyer L, Dedeken P. Cost Effectiveness of Lacosamide in the Adjunctive Treatment of Patients with Refractory Focal Epilepsy in Belgium. CNS Drugs. 2012 2012/04/01;26(4):337-350.

62. Vera-Llonch M, Brandenburg NA, Oster G. Cost-effectiveness of add-on therapy with pregabalin in patients with refractory partial epilepsy. Epilepsia. 2008 Mar;49(3):431-7.

63. Pathak SJ, Shah VB. Sudden Unexpected Death in Epilepsy. StatPearls. Treasure Island (FL): StatPearls Publishing; 2021.

64. Office of National Statistics. National life tables: England, 1980-1982 to 2016-2018. ONS, 2020. Available at: https://www.ons.gov.uk/file?uri=/peoplepopulationandcommunity/birthsdeat
65. Park KM, Kim SE, Lee BI. Antiepileptic drug therapy in patients with drug-resistant epilepsy. Journal of Epilepsy Research. 2019;9:14-26.

66. Shorvon SD, Löwenthal A, Janz D, et al. Multicenter Double-Blind, Randomized, Placebo-Controlled Trial of Levetiracetam as Add-on Therapy in Patients with Refractory Partial Seizures. Epilepsia. 2000;41(9):1179-1186.

67. Brodie MJ. Outcomes in newly diagnosed epilepsy in adolescents and adults: Insights across a generation in Scotland. Seizure. 2017 Jan;44:206-210.

68. Gidal BE. Do New Antiepileptic Drugs with Novel Mechanisms of Action Suggest Reconsideration of Rational Polypharmacy? US Neurology. 2010;06(01).

69. Husain A, Chung S, Faught E, et al. Long-term safety and efficacy in patients with uncontrolled partial-onset seizures treated with adjunctive lacosamide: results from a Phase III open-label extension trial. Epilepsia. 2012 Mar;53(3):521-8.
Table 1. Model population characteristics

| Parameter               | Base-case value                                                                 | Source                  |
|-------------------------|---------------------------------------------------------------------------------|-------------------------|
| Indicated population    | Adults and children with focal seizures, refractory to ASMs and not suitable candidates for surgery | [25,26]                  |
| Percentage adults       | 94.5%                                                                           | Individual patient data from E03 and E05 [27] |
| Mean starting age       | 33.2 (years)                                                                   | [25,26]                  |
| Sex (% male)            | 52.5%                                                                           | [25,26]                  |
| Baseline HRQoL          | Varied by age and weighted by gender                                            | [28,29]                  |

**Abbreviations:** ASM, anti-seizure medication; HRQoL, health-related quality of life.
Table 2. Clinical effectiveness transition probabilities

| Parameter | Base-case transition probability value | Lower bound | Upper bound |
|-----------|----------------------------------------|-------------|-------------|
|           | Value sets used for DSA \(^a\)          |             |             |
|           | VNS patients:                           |             |             |
|           | <50% (no response): 0.742               | 0.853       | 0.630       |
|           | 50-74% (responder): 0.166               | 0.094       | 0.237       |
|           | 75-99% (responder): 0.086               | 0.049       | 0.123       |
|           | 100% (seizure free): 0.007              | 0.004       | 0.009       |
|           | ASM only patients:                      |             |             |
|           | <50% (no response): 0.843               | 0.969       | 0.716       |
|           | 50-74% (responder): 0.138               | 0.027       | 0.250       |
|           | 75-99% (responder): 0.019               | 0.004       | 0.034       |
|           | 100% (seizure free): 0.000              | 0.000       | 0.000       |

Relative increase in responders and seizure free patients that informed long-term health state transition probabilities (3-24 months) for VNS patients \(^b\) [32]

| At end of 3 months: | % responders: 40% | 34% | 46% |
|                     | % seizure free: 2.6% | 2.2% | 3.0% |

Cycle-adjusted probabilities applied between 3 and 24 months (derived from Englot et al. data) for VNS patients \(^c\)

| From <50% (no response) to: | <50% (no response): 0.954 | 0.965 | 0.940 |
|                             | 50-74% (responder): 0.030 | 0.023 | 0.039 |
|                             | 75-99% (responder): 0.015 | 0.011 | 0.019 |
|                             | 100% (seizure free): 0.001 | 0.001 | 0.001 |

From 50-74% (responder) to:
| Health State | Probability 1 | Probability 2 | Probability 3 |
|--------------|--------------|--------------|--------------|
| 50-74% (responder) | 0.935 | 0.935 | 0.935 |
| 75-99% (responder) | 0.052 | 0.052 | 0.052 |
| 100% (seizure free) | 0.012 | 0.013 | 0.012 |

| Health State | Probability 4 | Probability 5 |
|--------------|--------------|--------------|
| From 75-99% (responder) to: | 0.987 | 0.988 |
| 75-99% (responder) | 0.988 | 0.013 | 0.012 |
| 100% (seizure free) | 0.012 |

Long-term health state transitions for ASM patients

Assumed patients remain in same health state after 3 months

Abbreviations: ASM, anti-seizure medication; DSA, deterministic sensitivity analysis; VNS, vagus nerve stimulation.

Notes:  
a. Probabilities have been rounded to three decimal places. The DSA for transition probabilities involved setting all transition probabilities simultaneously to the lower bound, or to the upper bound.

b. Upper and lower bounds are based on an assumed +/- 15% difference from the mean, with lower bound values selected to give a worse disease response, and upper bound values selected to give better disease response. All transition probabilities are varied simultaneously as a single set.

c. Informed also by assuming that 64%, 33% and 3% of patients who achieve a response from the <50% reduction (no response) state over the 3-24 month period would move to the 50-74% (responder), 75-99% (responder), and 100% (seizure free) percentage reduction health states, respectively. These proportions were derived from the resulting distribution of the responder VNS patients at 3 months in the E03 and E05 trials. The estimated transition probabilities were calibrated to align with the relative increase in response and seizure freedom calculated from the Englert et al. data reported above.
Table 3. Proportion of patients experiencing treatment related adverse events

| Parameter   | Year 1          | Year 2          | Year 3+         |
|-------------|-----------------|-----------------|-----------------|
|             | Mean (range for DSA) |                |                  |
| Hoarseness  | 0.29 (0.243 to 0.335) | 0.19 (0.134 to 0.246) | 0.02 (0.000 to 0.049) |
| Cough       | 0.08 (0.052 to 0.104) | 0.06 (0.025 to 0.093) | 0.016 (0.000 to 0.041) |
| Dyspnoea    | 0.08 (0.053 to 0.107) | 0.03 (0.006 to 0.054) | 0.03 (0.000 to 0.065) |

*Source: Morris et al 1999 [33]. Abbreviations: DSA, deterministic sensitivity analysis.*

Table 4. Health state utilities

| Parameter | Corresponding seizure frequency group reported in Messori et al. [22] | Mean utility *a* | Range for DSA |
|-----------|-------------------------------------------------|-----------------|---------------|
| 0-50% reduction (no response) | 10+ per month | 0.66 | 0.65 to 0.67 |
| 50-74% reduction (responder) | 2-9 per month | 0.79 | 0.78 to 0.80 |
| 75-99% reduction (responder) | 0-1 per month | 0.91 | 0.90 to 0.92 |
| 100% reduction (seizure free) | 0 seizures per year | 0.96 | 0.95 to 0.97 |

Baseline for population *b* 0.92 *b* -

*Abbreviations: DSA, deterministic sensitivity analysis. Notes: a, mean values displayed are as reported by or derived from the literature. These are used to understand the relative difference between model health states; b, this value represents the age- and gender ratio-adjusted baseline for ‘seizure free’ patients to which the relative utility differences between health states should be applied. Over the time horizon, this baseline utility value was continuously adjusted according to the patients’ mean age.*

Table 5. VNS adverse events disutilities

| Parameter               | Mean         | Upper and lower limit for DSA *a* |
|-------------------------|--------------|-----------------------------------|
| Dyspnoea disutility [40]| 0.05         | 0.043 to 0.058                    |
| Cough disutility [40]   | 0.046        | 0.039 to 0.053                    |
| Hoarseness disutility [41]| 0.02      | 0.017 to 0.023                    |

*Abbreviations: DSA, deterministic sensitivity analysis. Notes: a, ranges calculated based on an assumed +/- 15% difference from the mean.*
Table 6. Unit costs for health state care items

| Item                                                                 | Activity level | Base-case cost* [43] | Range for DSA † |
|---------------------------------------------------------------------|----------------|-----------------------|-----------------|
| A&E visits *                                                       | 20,380,060     | £166                  | £98 to £442     |
| Non-elective inpatient admission: epilepsy b                      | 191,787        | £1,340                | £357 to £5,165  |
| Elective inpatient admission: epilepsy b                           | 4,688          | £3,777                | -               |
| Day case for epilepsy b                                            | 29,667         | £587                  | -               |
| Elective inpatient admission for epilepsy, incl. day cases [43] b   |                | £1,022                | £549 to £7,746  |
| Neurologist appointment [43] c                                      | Adult: 1,223,726 | Mixed: £186          | -               |
|                                                                     | Child: 30,867  | Adult: £185           | Adult: £47 to £245 |
|                                                                     |                | Child: £203           | Child: £72 to £254 |
| GP visits [42]                                                     |                | £39                   |                 |
| Insertion of neurostimulator for Treatment of Neurological Conditions [43] d | Adult: 876 | Mixed: £6,987          | -               |
|                                                                     | Child: 149     | Adult: £6,986          | Adult: £146 to £7,715 |
|                                                                     |                | Child: £7006           | Child: £5,747 to £12,358 |

Abbreviations: A&E, Accident and Emergency; DSA, deterministic sensitivity analysis. GP, general practitioner; HRG, healthcare resource group. Notes: *, weighted average for adult and paediatric population; †, ranges calculated using either all minimum or all maximum values possible for each HRG code; a, HRG codes VB01Z to VB09Z and VB11Z; b, HRG codes AA26C to AA26H which relate to people with ‘Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury’ and is weighted accordingly for all comorbidity levels; c, Consultant led for service code 400 and 223; d, HRG code AA60A and AA60B.
Table 7. Summary of annual health care resource utilisation

| Health care resource item | Health state | Mean (range for DSA) |
|---------------------------|--------------|----------------------|
|                           |              | 100% seizure reduction (seizure free) a | 75%-99% seizure reduction | 50-74% seizure reduction | <50% seizure reduction |
|                           |              | Mean (range for DSA) | Mean (range for DSA) | Mean (range for DSA) | Mean (range for DSA) |
| Mean seizure frequency from E03 and E05 | 0 | 243 | 287 | 506 |
| A&E visits                | 0.00 | 1.35 | 1.60 | 4.89 |
|                           |       | (1.15 to 1.56) | (1.36 to 1.84) | (3.53 to 6.46) |
| Inpatient visits          | 0.00 | 1.25 | 1.48 | 6.12 |
|                           |       | (1.06 to 1.44) | (1.26 to 1.7) | (4.42 to 8.10) |
| Inpatient non-elective    | 0.00 | 1.04 | 1.22 | 5.06 |
|                           |       | (0.88 to 1.19) | (1.04 to 1.41) | (3.66 to 6.70) |
| Inpatient elective        | 0.00 | 0.22 | 0.26 | 1.06 |
|                           |       | (0.18 to 0.25) | (0.22 to 0.29) | (0.76 to 1.40) |
| Outpatient neurologist visits | 1.50 | 7.45 | 8.81 | 16.63 |
|                           |       | (1.28 to 1.73) | (6.34 to 8.57) | (7.49 to 10.13) | (11.58 to 21.19) |
| GP visits                 | 0.15 | 2.58 | 3.02 | 5.21 |
|                           |       | (0.11 to 0.20) | (2.54 to 2.63) | (2.98 to 3.07) | (5.17 to 5.26) |

Abbreviations: A&E, accident and emergency; DSA, deterministic sensitivity analysis; GP, general practitioner. Notes: source references for resource use by health state are shown in each column heading. a, assumption based on current English clinical guidance [4], which advises that all epilepsy patients should have at least one annual review, with an assumed increase in the neurologist frequency to account for ASM regimen adjustments.

Table 8. Annual costs per health state

| Resource    | 100% seizure reduction (seizure free) | 75-99% seizure reduction | 50-74% seizure reduction | <50% seizure reduction |
|-------------|---------------------------------------|--------------------------|--------------------------|------------------------|
| A&E         | £0                                    | £225                     | £266                     | £811                   |
| Inpatient   | £0                                    | £1,609                   | £1,902                   | £7,866                 |
| Outpatient  | £279                                  | £1,387                   | £1,639                   | £2,981                 |
| GP          | £6                                    | £101                     | £119                     | £205                   |

Abbreviations: A&E, accident and emergency; GP, general practitioner
| Parameter | Cost for base case | Source |
|-----------|------------------|--------|
| [A] VNS therapy device, lead and tunneler | £13,846 | Weighted average of Aspire 106 and Sentiva NHS supply chain framework price (data on file) |
| [B] VNS therapy device | £11,119 | NHS Reference cost incorporating: |
| | | - Surgical placement of lead; |
| | | - Placement of electrical pulse generator; |
| | | - Surgical assistance; |
| | | - Anaesthetics; |
| | | - Adverse events associated with procedure; |
| | | Weighted by proportion of adults in the cohort. |
| [C] Implant, explant and replacement procedure | Adults and children: £6,987 | Two outpatient reviews assumed with neurosurgeon (service code 150, activities 305,955; mixed between consultant and non-consultant led) or paediatric neurology (service code 421, activities 83,770); one preoperatively and one post operatively (i.e. programming reviews) |
| | | Cost of one adult review = £183 |
| | | Cost of one child review: £203 |
| [D] Pre- and post-operative neurosurgeon review | Adults and children: £372 | Calculated using the following: |
| | | - Number of clinicians per procedure: 2 |
| | | - Cost of 1 hour of clinician time: £109 (PSSRU 2020) [42] |
| | | - Hours of training per annum required: 7.5 |
| | | - Number of VNS procedures undertaken per annum: 50 |
| [E] Clinician training | Adults and children: £33 | Implantation = [A+C+D+E] = £ 21,238 |
| | | Replacement = [B+C+D+E] = £ 18,511 |
| | | Explant = [C+D+E] = £ 7,392 |

**Abbreviations:** NHS, National Health Service; VNS, vagus nerve stimulation.
Table 10. Costs associated with adverse events

| Adverse event | Resources | Costs | Total-cycle adjusted cost for a patient experiencing a given event |
|---------------|-----------|-------|------------------------------------------------------------------|
| Dyspnoea / Hoarseness / Cough | 1 neurologist visit and GP visit per year assumed for 1-year continuous adverse event | Neurologist: £186 [43] GP: £39 [42] | £56 |

**Abbreviations:** GP, general practitioner.

Table 11. Base-case cost-effectiveness results

|                         | VNS + ASM | ASM alone | Increment |
|-------------------------|-----------|-----------|-----------|
| **Costs**               |           |           |           |
| Device cost: implant procedure | £21,238   | £0        | £21,238   |
| Device cost: explantation | £126      | £0        | £126      |
| Device cost: replacement | £7,186    | £0        | £7,186    |
| ASM acquisition costs   | £22,925   | £22,925   | £0        |
| TRAE costs              | £203      | £0        | £203      |
| Acute care costs        | £4,689    | £6,090    | -£1,401   |
| Inpatient costs         | £43,386   | £58,176   | -£14,790  |
| Outpatient costs        | £19,345   | £23,220   | -£3,874   |
| Primary care costs      | £4,344    | £1,601    | -£258     |
| Total costs             | £120,441  | £112,011  | £8,430    |
| **Health outcomes**     |           |           |           |
| Life years              | 8.387     | 8.387     | 0         |
| QALYs                   | 6.118     | 5.642     | 0.476     |

**Incremental outcomes**

| Incremental net monetary benefit (£20,000 threshold) | £1,089 |
| Incremental net health benefit (£20,000 threshold) | 0.05 |

**Abbreviations:** ASM, anti-seizure medication; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TRAE, treatment-related adverse event; VNS, vagus nerve stimulation.
### Table 12. Deterministic sensitivity analysis

| Parameter or parameter group tested | Base-case value | Low value(s) | High value(s) | ICER | Range for DSA |
|-------------------------------------|-----------------|--------------|---------------|------|---------------|
| **For low value(s)** | | | | | £17,711 |
| **For high value(s)** | | | | | |
| **Base case** | | | | | |
| Health state utilities | Multiple | Lower limits | Upper limits | £17,409 | £18,300 |
| TRAE probabilities | Multiple | Lower limits | Upper limits | £16,985 | £18,621 |
| TRAE disutilities | Multiple | Lower limits for all TRAEs | Upper limits for all TRAEs | £17,553 | £17,872 |
| Health state transition probabilities for VNS and ASM only arms | Multiple | Lower limits for all transitions | Upper limits for all transitions | £9,816 | £26,059 |
| Long-term health state transition probabilities | Multiple | Lower limits | Upper Limits | £25,211 | £10,933 |
| Mortality: SMR | 2.2 | 1.97 | 2.47 | £17,687 | £17,763 |
| VNS battery replacement probabilities | Extrapolation function | Lower limits for extrapolation coefficients | Upper limits for extrapolation coefficients | £17,454 | £17,944 |
| VNS explantation probabilities | Extrapolation function | Lower limits for extrapolation coefficients | Upper limits for extrapolation coefficients | £16,726 | £49,623 |
| ASM reduction with VNS, as ratio compared to ASMs only | 1.0 | 0.85 | 1.15 | £13,450 | £21,973 |
| Inpatient admission unit costs | Multiple | Minimum values for each HRG | Maximum values for each HRG | £39,357 | VNS DOM |
| Outpatient consultant visit unit cost | £186 | £49 | £245 | £22,650 | £15,581 |
| A&E unit cost | £166 | £98 | £442 | £18,922 | £12,818 |
| VNS procedure unit costs | £6,987 | £454 | £7,971 | VNS DOM | £20,614 |
| Inpatient resource use | Multiple | Lower limits | Upper limits | £27,248 | £6,454 |
| Outpatient/GP resource use | Multiple | Lower limits | Upper limits | £20,780 | £13,990 |
| A&E resource use | Multiple | Lower limits | Upper limits | £18,656 | £16,589 |
| VNS device cost | £11,119 | £9,451 | £12,786 | £11,988 | £23,435 |
| VNS training cost | £33 | £28 | £38 | £17,674 | £17,762 |
| Implant cost | £21,238 | £18,052 | £24,423 | £11,018 | £24,404 |
| Explant cost | £7,392 | £6,283 | £8,501 | £17,671 | £17,751 |
| Replacement cost | £18,511 | £15,734 | £21,287 | £15,447 | £19,976 |

**Abbreviations:** A&E, hospital accident & emergency department; ASM, anti-seizure medication; DSA, deterministic sensitivity analysis; GP, general practitioner; HRG, healthcare resource group code; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SMR, standardized mortality ratio;
TRAE, treatment-related adverse event; VNS, vagus nerve stimulation; VNS DOM, VNS+ASM treatment dominates ASM only treatment.