National Institute for Health and Care Excellence

FINAL

Epilepsies in children, young people and adults: diagnosis and management

[14] Evidence review: Vagus nerve stimulation

NICE guideline NG217

Evidence reviews underpinning recommendations 8.3.1 and 8.3.2 and a research recommendation in the NICE guideline

April 2022

FINAL

Developed by the National Guideline Centre

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and, where appropriate, their carer or guardian.

Local commissioners and providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN: 978-1-4731-4513-9

Contents

1 Vagus nerve stimulation

1.1 Review question

What is the effectiveness of vagus nerve stimulation in epilepsy?

1.1.1 Introduction

Vagal nerve stimulation (VNS) is a surgical treatment option for patients with pharmacoresistant epilepsy. VNS therapy is considered an option for selected people, with the aim of reducing seizure frequency and intensity and improving quality of life, although it is unlikely to result in seizure freedom. A pulse generator is surgically implanted with electrodes applied to the left vagus nerve. The VNS therapy device then delivers repeated electrical stimulations to the vagus nerve. The technology and size of devices have improved over the years, although VNS is not without its own risks and side effects. This chapter examines the clinical and cost-effectiveness evidence of the VNS procedure.

1.1.2 Summary of the protocol

Table 1: PICO characteristics of review question

Population	Children, young people and adults with confirmed pharmacoresistant epilepsy Strata: evidence in people with learning disabilities will be presented separately from evidence in people without learning disabilities (to be analysed separately)
Interventions	High frequency vagus nerve stimulation Low frequency vagus nerve stimulation Auto stimulation (rapid cycling) and SenTiva device
Comparisons	Sham or usual care One vagus nerve stimulation method vs different vagus nerve stimulation method
Outcomes	**Critical** • Mortality at short-term follow-up of 12 months and longer-term follow-up of up to 60 months • Seizure freedom (100% reduction in seizure frequency) at short-term follow-up of 12 months and longer-term follow-up of up to 60 months • Seizure frequency (50% or greater reduction in seizure frequency) at short-term follow-up of 12 months and longer-term follow-up of up to 60 months • Quality of life (measured with a validated scale) at short-term follow-up of 12 months and longer-term follow-up of 60 months • Healthcare resource use • Social functioning (measures of adaptive functioning or adaptive behaviour using a validated scale) short-term follow-up of 12 months and longer-term follow-up of up to 60 months • Cognitive outcomes (including neuropsychological measures of global cognitive functioning, executive functioning and memory using a validated scale) short-term follow-up of 12 months and longer-term follow-up of up to 60 months • In children and young people: neurodevelopmental outcomes (behavioural and emotional outcomes measured with a validated scale) short-term follow-up of 12 months and longer-term follow-up of up to 60 months • Adverse events (analysed separately): ○ lead fracture ○ infection ○ hoarse voice

	○ cardiac difficulties ○ device removal
Study design	• Randomised controlled trials (RCTs) • Systematic reviews of RCTs If no RCTs are found for a particular intervention, prospective observational comparative studies will be considered only if they adjust for the key confounders of age of epilepsy onset, classification (focal, generalised, or epilepsy syndrome), earlier invasive epilepsy surgery, number of AEDs tried prior to intervention, AED changes recorded during intervention reporting, gender, mental health and learning disability.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[64] Methods specific to this review question are described in the review protocol in Appendix A:.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A search was conducted for randomised control trials (RCTs) comparing the effectiveness of high-frequency vagus nerve stimulation (VNS), low-frequency VNS or auto stimulation and SenTiva device versus sham, usual care or one VNS method to another VNS method.

Five studies were included in the review;[7, 39, 41, 45, 61, 70, 76, 77] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below). The comparisons included are:

- High VNS versus low VNS (n=3)
- VNS + Best medical practice versus best medical practice (n=1)
- High transcutaneous VNS (tVNS) versus low tVNS (n=1)

See also the study selection flow chart in Appendix C:, study evidence tables in Appendix D:, forest plots in Appendix E:, and GRADE tables in Appendix F:.

1.1.4.2 Excluded studies

Two Cochrane reviews[66,69] were identified and assessed for inclusion by assessing the studies included individually and comparing it to our protocol. All the individual studies included in these reviews did not match our protocol in terms of length of follow up as it was for less than a year.

Nonetheless, they were included when possible if they had any adverse events that met the protocol.

See the excluded studies list in Appendix I:.

1.1.5 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Bauer 2016[7]	High level frequency transcutaneous vagus nerve stimulation (tVNS), n=37 Versus Low level frequency transcutaneous vagus nerve stimulation (tVNS, active control), n=39	Adults with confirmed pharmacoresistant epilepsy (Patients between 18 and 65 years of age were eligible) Germany Mean age (SD) – 38.8 (12.5)	Adverse events - cardiac difficulties	
Handforth 1998[41]	High frequency vagus nerve stimulation (VNS), n=95 Versus Low frequency vagus nerve stimulation (VNS), n=103	Young people and adults with confirmed pharmacoresistant epilepsy (People aged 12 to 65 years were eligible) USA Mean age (SD) High group = 32.1 (10.8) Low group = 34.2 (10.1)	Adverse events - infection	
Holder 1992[45] Merged with Salinksy 1995[77], George 1994[39] and Ramsay 1994[70]	High frequency vagus nerve stimulation (VNS), n=54 Versus Low frequency vagus nerve stimulation (VNS), n=60	Young people and adults with confirmed pharmacoresistant epilepsy (People aged 12 to 60 years were eligible) Multiple countries	Adverse events - Hoarseness - Cardiac difficulties - Infection	

Study	Intervention and comparison	Population	Outcomes	Comments
		Mean age (range) High group = 34.7 (21.1 to 57.4) Low group = 33 (19.7 to 51.4)		
Michael 1993[61]	High frequency vagus nerve stimulation (VNS), n=10 Versus Low frequency vagus nerve stimulation (VNS), n=12	Young people and adults with confirmed pharmacoresistant epilepsy Multiple countries Mean age (range) = 32 (15 to 56)	Adverse events - Hoarseness	
PULSE study 2014[76] (Ryvlin 2014)	Vagus nerve stimulation (VNS) and best medical practice (BMP), n=48 Versus Best medical practice (BMP), n=48	Young people and adults with confirmed pharmacoresistant epilepsy (People aged between 16 to 75 years were eligible) Multiple countries Mean age (SD) VNS and BMP = 38 (13) BMP = 41 (11)	Cognitive outcome - Clinical global impression of improvement scale (CGI-I) Neurological outcome - Neurological disorders depression inventory in epilepsy scale (NDDI-E) - Seizure frequency (50% or greater reduction in seizure frequency) Quality of life - Quality of Life in Epilepsy Inventory - 89 (QOLIE-89) scale Adverse events - Cardiac difficulties (measured at 1 year)	BMP was defined as the individualized therapy judged optimal by investigators at each visit for each patient, which could include a change in dosage or type of ASMs (including their withdrawal).

See Appendix D: for full evidence tables.

1.1.6 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: High VNS versus Low VNS

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with High VNS versus Low VNS (95% CI)
Adverse events - infection	265 (2 studies) 14-16 weeks	LOW[a] due to imprecision	RR 0.94 (0.45 to 1.94)	101 per 1000	6 fewer per 1000 (from 55 fewer to 95 more)
Adverse events - cardiac difficulties (chest pain, shortness of breath)	67 (1 study) 14 weeks	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.16 (0.17 to 7.77)	56 per 1000	9 more per 1000 (from 46 fewer to 376 more)
Adverse events - hoarseness	136 (2 studies) 14 weeks	VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision	RR 1.73 (0.61 to 4.94)	181 per 1000	132 more per 1000 (from 70 fewer to 711 more)

a Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
b Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
c Downgraded by 1 or 2 increments because the point estimate and or the confidence intervals varied widely across studies, unexplained by subgroup analysis.

Table 4: Clinical evidence summary: VNS + BMP versus BMP

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with VNS + best medical practice versus best medical practice (95% CI)
Quality of life Quality of Life in Epilepsy Inventory - 89 (QOLIE-89) scale. Scale from: 0 to 89. Higher score is good.	60 (1 study) 1 years	VERY LOW[a,b] due to risk of bias, imprecision		The mean quality of life in the control groups was 1.2	The mean quality of life in the intervention groups was 4.3 higher (0.73 to 7.87 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with VNS + best medical practice versus best medical practice (95% CI)
Proportion of people with >50% decrease in seizure frequency	60 (1 study) 1 years	VERY LOW[a,c] due to risk of bias, imprecision	RR 1.34 (0.59 to 3.04)	241 per 1000	82 more per 1000 (from 99 fewer to 492 more)
Clinical global impression of improvement scale (CGI-I). Scale from: 0-7. Lower score is good.	60 (1 study) 1 years	VERY LOW[a,c] due to risk of bias, imprecision		The mean cognitive outcome in the control groups was -0.3	The mean cognitive outcome in the intervention groups was 0.5 lower (0.99 to 0.01 lower)
Neurological outcome Neurological disorders depression inventory in epilepsy scale (NDDI-E). Lower score is good.	60 (1 study) 1 years	VERY LOW[a,b] due to risk of bias, imprecision		The mean neurological outcome in the control groups was -0.2	The mean neurological outcome in the intervention groups was 0.8 lower (2.26 lower to 0.66 higher)
Adverse events - cardiac difficulties (chest pain)	96 (1 study) 1 years	LOW[a,b] due to risk of bias, imprecision	Peto OR 7.71 (0.78 to 75.97)	0 per 1000	60 more per 1000 (from 10 fewer to 140 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c Downgraded by 1 increment as the confidence interval crossed one MID of -0.55
d Downgraded by 1 increment as the confidence interval crossed one MID of -0.17

Table 5: Clinical evidence summary: High tVNS versus Low tVNS

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with High tVNS versus Low tVNS (95% CI)
Adverse events - Cardiac difficulties	76 (1 study) 20 weeks	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.14 (0 to 7.19)	26 per 1000	30 fewer per 1000 (from 90 fewer to 40 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

See Appendix F: for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

No health economic studies were included.

1.1.7.2 Excluded studies

Three economic studies relating to this review question were identified but were excluded due to a combination of limited applicability and methodological limitations.[27, 37, 38, 52, 53] These are listed in Appendix I:, with reasons for exclusion given. The treatment effects used in these studies were from studies that have been excluded from the clinical review.

Two economic studies[16],[12] related to this review were included in the 2004 Epilepsies guideline, however the dates of these studies are prior to the date cut-off for economic evidence, and these have been excluded, but are listed in Appendix I: for clarity.

See also the health economic study selection flow chart in Appendix G:.

1.1.8 Health economic modelling

This review question was not prioritized for de novo economic modelling. However, to aid in decision making a threshold analysis was performed and presented to the committee.

As this threshold analysis is far simpler than a full cost-utility analysis for this review question would be, it should not be viewed as a substitute. However, as no health economic studies were included in this review and as this question was not prioritized for de novo economic modelling, such analyses add value to the decision-making process; by helping the committee to conceptualize a problem they would otherwise have to address, without any such analysis.

1.1.9 Unit costs

Some costs of the VNS devices are illustrated in the table below. These have been sourced through a committee member.

Table 6: UK costs of Vagal nerve stimulation pulse generators

Component	Description	Cost
Costs per procedure		
1 x Generator (VNS stimulator device)	Newer models: *SenTiva ™ Generator, Model 1000 (single pin receptacle, volume 8cc)* Older models: *Pulse™ Generator, Model 102 (single pin receptacle, volume 14cc)*	£10,423 £7,428
1 x Implantable lead	*PerenniaDURA™ Lead, Model 303 (single pin)* A lead transmits the stimulation pulse from the generator to the left vagus nerve.	£2,275
1 x tunnelling tool	*Tunneler, Model 402* A disposable surgical tool used for subcutaneous tunnelling of the lead from the nerve site	£133

Component	Description	Cost
1 x patient essentials pack	*Patient Essentials Patient Kit, Model 220* A kit containing one Model 220-3 Magnet (watch style), one Model 220-4 Magnet (pager style), and two Patient Emergency Information Cards.	£92
TOTAL		**Newer model: £12,923.00** **Older model: £9,928.00**
Costs spread over many procedures (a)		
Accessory pack	*Accessory Pack, Model 502* A pack containing sterile back-up components sometimes needed for VNS Therapy implant and removal. Contains a single pin and a dual pin generator resistor assembly, a hex screwdriver and lead tie downs.	£403
VNS wand	*Programming Wand, Model 2000* A telemetry wand that transmits programming information from the computer to the generator.	£2,414
Tablet	*Software model 3000 with programming tablet* Programming software and tablet which interrogates the generator and modifies the stimulation parameters.	£2,250

Source: Through committee member hospital price list. Note all components are from Liva Nova. The committee were used for sources of device costs rather than the NHS supply chain, as that did not contain the older models of the generator. Of note, there may be some variation in prices between the NHS supply chain and hospital list prices. More commonly, hospital list prices will be slightly cheaper than prices cited in the NHS supply chain catalogue.
(a) The cost per patient would depend on the number of uses and lifespan of the products.

There may be additional components needed apart from the main device itself. The battery needs to be replaced after a certain number of years (typically every three to five years) which involves a re-operation. There will also be follow up costs such as seeing a consultant to discuss the effectiveness and settings of the device.

As well as the cost of the device, there is the surgical cost of implanting the device:

Table 7: NHS reference costs – cost of implantation of VNS device.

Currency code	Currency description	Activity	Unit cost
AA60A	Insertion of Neurostimulator for Treatment of Neurological Conditions, 19 years and over	1,760	£3,601
AA60B	Insertion of Neurostimulator for Treatment of Neurological Conditions, 18 years and under	214	£5,419

Source: NHS reference costs 2019/20. HRG code identified by mapping the OPCS code from the coding recommendations in the NICE interventional procedure guidance on Vagus nerve stimulation for refractory epilepsy in children (IPG50).[65]

1.1.9.1 Other calculations

Using data from the clinical review on the additional people with >50% decrease in seizure frequency [76] and utility values, it is possible to estimate an approximate QALY gain.

Table 8: Quality adjusted life year gain (QALY) from the addition of VNS

Scenario	Additional people with >50% decrease in seizure frequency at 1 year	Gain in QoL (utility) per person	Incremental QALY gain per 1000 people	Incremental QALY gain per person
1. No assumptions made beyond 12 months data.	Additional 82 per 1000 (d)	0.18 (a)	14.9 (b) (0.18*82 people)	0.0149
2. Assuming gain is sustained for the lifetime of the person (c)	Additional 82 per 1000 (d)	0.18 (a)	270.1 (0.18*82 people *18.1 years)	0.2701

(a) Where the utility of a non-responder was 0.623 and the utility for a patient who has between 50-99% reduction in seizure frequency being 0.805 – See Economic analysis report on the cost effectiveness of resective surgery.
(b) This is assuming that utility gain is experienced from the very beginning after having VNS.
(c) Life expectancy for patient with drug-resistant epilepsy receiving medical management is 31.7 years (18.1 years discounted at 3.5% per year to reflect time preference). See Economic analysis report on the cost effectiveness of resective
(d) From Table 4 Clinical evidence summary: VNS + BMP versus BMP

Using this rough estimate of QALY gain from the addition of VNS to best medical practice (BMP), and by re-arranging the Cost per QALY gained (ICER) equation, we can work out the maximum cost difference between VNS + BMP and BMP that would make VNS + BMP an effective use of NHS resources, assuming QALYs are valued at £20,000 each. .

Cost-effectiveness criterion

The equations detailed below show the Cost per QALY gained (ICER) equation and the manipulation of this equation to obtain the maximum cost difference which would make VNS + BMP borderline cost effective.

$$Cost\ per\ QALY\ gained\ threshold = \frac{Total\ cost_{\ VNS} - Total\ cost_{\ BMP}}{Total\ QALYs_{\ VNS} - Total\ QALYs_{\ BMP}}$$

In other words,

$$Cost\ per\ QALY\ gained\ threshold = \frac{Difference\ in\ costs}{Difference\ in\ QALYs}$$

The maximum cost difference (referred to in health economics as the incremental costs) between VNS + BMP and BMP that would make VNS + BMP borderline cost effective is calculated by

$$Difference\ in\ costs = Cost\ per\ QALY\ gained\ threshold \times Diffrence\ in\ QALYs$$

The cost per QALY gained threshold set by NICE is £20,000. However, in specific instances interventions which fall between a £20,000 and £30,000 cost per QALY gained threshold will be recommended.

Results: Maximum cost difference that is consistent with Vagus Nerve Stimulation being cost effective

The results were calculated using the incremental QALY gains per person (Table 8) for a one-year time horizon and a lifetime horizon. These utility values were multiplied by NICE's Cost per QALY gained threshold to obtain the maximum cost difference which would make VNS + BMP borderline cost effective.

Scenario 1 (one-year time horizon): £20,000 * 0.0149 = £298

£30,000 * 0.0149 = £448

Scenario 2 (lifetime horizon): £20,000 * 0.2701 = £5,402

£30,000 * 0.2701 = £8,104

Therefore, assuming the improvement in seizure status is sustained up until death it can be inferred that the maximum difference in costs, or incremental costs, for VNS and BMP, is £5,402 at a threshold of £20,000 per QALY (or £8,104 at £30,000 per QALY).

It is important to note that in a full cost effectiveness analysis the costs and effects of VNS and BMP would likely be modelled over a lifetime horizon. Therefore, the long-term costs and outcomes of VNS + BMP and BMP would be compared – taking into account the impact of resource use and costs associated with improved outcomes of VNS. Thus, it is not appropriate to directly compare the maximum difference in costs, or incremental cost of £5,402 to the cost of the VNS device (and implantation costs) reported in section 1.1.9.

The committee noted that the outcome 'seizure freedom' was not reported in the RCT data used to estimate total QALYs (Table 8). Therefore, the estimate of QALYs gains was only based on the outcome 'reduction in seizure frequency'. The RCT data also only reported outcomes up to one year and the committee highlighted the effectiveness of VNS improves over time. The committee therefore acknowledged that the QALYs used in the analysis are likely an underestimation of the true QALY gains observed. If the true QALY gains observed are greater, the maximum incremental cost difference which make VNS + BMP cost effective will also be higher. Subsequently allowing the cost of VNS + BMP to be greater. In other words, the higher the QALY gain the greater chance VNS + BMP has at being cost effective at NICE's £20,000 threshold.

Overall, because the maximum incremental cost of VNS + BMP and BMP was obtained via a threshold analysis (using RCT data with a one-year time horizon, which omitted seizure freedom as an outcome) the results need to be interpreted with caution – acknowledging there are a number of factors which will affect the incremental costs observed between the two strategies being compared. The committee's full discussion of this analysis is available in section 1.1.11.3.

1.1.10 Evidence statements

1.1.10.1 Clinical evidence statements

- None

1.1.10.2 Health economic evidence statements

- No relevant economic evaluations were identified.

1.1.11 The committee's discussion of the evidence

1.1.11.1 The outcomes that matter most

All outcomes were critical in this review, namely mortality, seizure freedom, seizure frequency, quality of life, healthcare resource social functioning, cognitive outcomes, and neurodevelopmental outcomes in children and young people. Where evidence was found, outcomes were assigned to either a follow-up of 12 months or a longer-term follow-up of up to 60 months. Additionally, adverse events at any time point were also included.

No evidence was identified for mortality, seizure freedom, healthcare resource use or social or cognitive functioning or neurodevelopmental outcomes in children and young people.

1.1.11.2 The quality of the evidence

Evidence from 5 RCTs evaluating vagus nerve stimulation (VNS) was identified. Three studies compared high-frequency VNS with low-frequency VNS. One study compared high-frequency transcutaneous VNS (tVNS; an external device that is applied intermittently to stimulate the auricular branch of the vagus nerve) versus low-frequency transcutaneous VNS, and one study compared VNS with best medical practice. The underlining principles of the technologies are the same – namely, antidromic stimulation of the vagus nerve will improve seizure profile. High VNS and high tVNS was considered the normal practice, while low VNS or low tVNS were considered comparable to no VNS or no tVNS. This is why the studies could be combined with VNS versus best medical practice when the committee was deliberating the evidence.

The evidence was of low or very low quality, mainly due to lack of allocation concealment, a high number of participants missing at the study follow up time-point and imprecision. Imprecision was noted for all outcomes. Inconsistency was present for hoarseness (adverse event) due to heterogeneity, and this remained unexplained by subgroup analysis.

The committee agreed to make a research recommendation to evaluate the effectiveness of VNS in people with epilepsy as little good-quality evidence had been identified. The committee agreed new research should more specifically evaluate outcomes in people with learning disabilities, as this patient population are more likely to proceed to VNS implantation in clinical practice than those without a learning disability.

The committee noted there was no robust long-term evidence on vagus nerve stimulation in epilepsy. The majority of the studies included were over 20 years old, all had small numbers of participants, and were of either low or very low quality.

The evidence for the outcomes of infection and cardiac difficulties showed no clinically important difference for high VNS compared with low VNS. A clinically important benefit of low VNS was found for one adverse event, hoarseness. The committee noted that the complication rates reported by the studies were not surprising for this intervention, given that more (electrical) current is delivered by high-frequency stimulation. They also discussed that high VNS is at greater frequency and, therefore, this may explain why there was a clinically important benefit of low VNS for one adverse event (hoarseness) compared to high VNS. For the comparison of VNS with best medical practice to best medical practice alone, a clinically important benefit of VNS combined with best medical practice was found for quality of life and proportion of people with a greater than 50% decrease in seizure frequency at one year. No clinically important difference was found for clinical global impression of improvement scale and neurological outcome. A clinically important benefit of best medical practice was found for the adverse event of cardiac difficulties. The committee noted the study was small and only reported outcomes at 12 months.

For high tVNS compared to low tVNS, there was only one outcome of adverse events, namely cardiac difficulties, which showed a clinically important benefit for high tVNS. The committee noted that tVNS is not used within the NHS.

Based on their own experience the committee agreed that anecdotally VNS appears to be effective. VNS tends to be considered a 'palliative' procedure for people who have trialled multiple anti-seizure medications and in whom resective surgery is not thought an option. The committee agreed that seizure freedom is not anticipated with the use of VNS, but there can be a reduction in seizure frequency or intensity and, as a consequence, lead to a better quality of life. The committee also noted that in their experience, most people who have VNS implantation return for battery replacements for their device, suggesting that they are finding some benefit through its use and wish to continue using the device. The committee noted that there might also be a slight placebo effect as a user unaware that their device has run out of power can continue to report a benefit from its use.

The committee agreed that a clinical benefit was more likely to be seen the longer VNS is used, but trials tend to report results too early (after 3 or 6 months), with the longest time-point reported was 1 year in one study. Clinical practice and opinion is that more benefit is likely to accrue much later after the device has been implanted.

The committee noted that paediatric populations may experience different outcomes from the use of VNS compared to adults due to starting VNS treatment at a much earlier age, and also parents or carers being better able to recognise seizures and swiping the magnet to offer additional stimulation earlier. It was also noted that VNS may not be an option for certain groups of patients, such as those with deteriorating neurological conditions leading to end of life or severe learning disabilities/challenging behaviour that prohibit practical use.

The committee noted that there is variation in current use but that it tends to be offered when anti-seizure medications have failed to control seizures and surgery is not suitable. There was no evidence to suggest that the use of Vagus nerve stimulation should stop for this small group with complex needs and few management options.

The committee agreed there was a lack of robust evidence for the use of VNS. There was also no evidence of harm with the use of VNS. Therefore, the committee decided it was appropriate to make a consensus recommendation based on their clinical experience to consider VNS in the small population of people with drug-resistant epilepsy and who are assessed as unsuitable for resective surgery. The committee discussed how some people and their families are keen to undergo the procedure because they have no further treatment options, even though the evidence to support the use of VNS is lacking. The committee discussed the importance of explaining to the person and their family or carer that the procedure is not risk-free, and that VNS implantation is unlikely to result in seizure freedom.

The committee acknowledged more evidence is needed to know how effective VNS is over a longer follow-up period and agreed to make a research recommendation.

1.1.11.3 Cost effectiveness and resource use

No economic evaluations were included in this review.

The committee noted that there was variation in current clinical practice with regards to the use of VNS but noted VNS tends to be offered to people with drug-refractory epilepsy where resective surgery is not an appropriate treatment option.

Unit costs of VNS were presented to the committee. The costs of the devices themselves were sourced from price lists from a committee member's hospital and relate to a particular manufacturer, but this is the most common device. The cost per patient can be upward of £10,000 for the device itself, and additional to this is the cost of the surgery to implant the device, which also costs several thousands of pounds. There may be other costs, such as

the potential need for video telemetry to identify if a person is a candidate for VNS (if they have not already had this earlier in the pathway). Ongoing costs include appointments to monitor the device, and any future battery changes, which would require another procedure. Batteries do not tend to last as long as might be expected, especially if the higher intensity setting is used, which consumes charge more quickly. The purpose of VNS is not to necessarily achieve seizure freedom, this is quite an unlikely outcome, but VNS reduces seizure frequency and the intensity of seizures, which can impact quality of life and lead to less resource use. It is also unlikely that people who have VNS would ever come off their ASMs; therefore, it is used as an adjunctive treatment. VNS does not have the side effects seen with ASMs, but infection is a concern. Over the longer-term management costs are anecdotally low, as people are already having monitoring appointments for their medications, and because the VNS-treated cohort are a complex group with uncontrolled epilepsy.

Threshold calculations were presented to the committee, using the single outcome identified from the review on effectiveness (seizure reduction - when comparing VNS in addition to best medical practice with no VNS), and combining this with quality-of-life values (related to living with seizures, and a reduction in seizures), to obtain an estimate of QALYs. This was then used in threshold calculations to work out the maximum incremental cost between strategies of VNS and no VNS that would make VNS cost effective. Two scenarios were demonstrated; one where no assumptions were made beyond the 1-year data from the clinical review, and another where the QALY gain was assumed to last a lifetime. These scenarios showed that the maximum cost difference between a strategy of VNS and no VNS was £298 and £5,402 respectively at NICE's £20,000 threshold (and £448 and £8,104 at NICE's £30,000 threshold).

It was discussed with the committee that is important not to directly compare the maximum cost differences of VNS and no VNS with the unit costs of VNS presented in section 1.1.9. This is because normally, in a full incremental cost effectiveness analysis the costs and effects of VNS and no VNS would likely be modelled over a lifetime horizon. Therefore, the long-term costs and outcomes of VNS and no VNS would be compared – taking into account the impact of resource use and costs associated with improved outcomes of VNS.

The committee noted that the outcome 'seizure freedom' was not reported in the RCT data used to estimate total QALYs (Table 8). Therefore, the estimate for QALYs gains was only based on the outcome 'reduction in seizure frequency'. The RCT data also only reported outcomes up to one year. The committee referenced a number of registry and case control studies which highlighted that the effectiveness of VNS improves over time; especially for those people who obtain a reduction in seizure frequency within the first six months of treatment. These studies also reported outcomes for 'seizure freedom', and although the proportion of people achieving seizure freedom with VNS was small, it's important to note this outcome was not reported in the RCT evidence used in our threshold calculations. Overall, because seizure freedom was omitted and other studies highlighted by the committee showed a greater long-term improvement in seizure reduction, the total lifetime QALYs calculated for our analysis are likely an underestimation of the true QALY gains observed. If the true QALY gains observed are greater, the maximum incremental cost difference which make VNS and no VNS borderline cost effective will also be higher. In other words, the higher the QALY gain the greater the probability VNS is cost effective at NICE's £20,000 threshold.

The committee also noted that the QoL weights used in the calculations may have uncertain generalisability to the population of interest but acknowledged no alternative QoL estimates were available.

Due to a lack of published health economic evidence identified for this review and the associated uncertainties and limitations with the threshold calculations, the committee concluded that they could only make a "consider" recommendation for the use of VNS for people with drug-resistant epilepsy (when surgery is not appropriate). The committee

qualitatively discussed the costs and benefits of VNS, noting VNS would likely be the most expensive strategy due to the high costs associated with the device and the need for monitoring and replacement of batteries in the device. The committee acknowledged in the short-to-medium term the levels of monitoring required for VNS and no VNS may not differ significantly because people with drug-refractory epilepsy require regular appointments to monitor their epilepsy. However, people receiving VNS would likely require fewer admissions to hospital as their seizures become better controlled. In addition, in the long-run, people receiving VNS may require fewer or shorter neurology appointments if they obtain seizure freedom or experience a significant reduction in their seizures.

The committee also noted people with drug resistant epilepsy experience significantly more comorbidities compared to those with controlled epilepsy (such as, depression, vascular disorders and neurological deficits). Therefore, the cost for people with drug resistant epilepsy may be particularly high if people experience complications or comorbidities associated with drug refractory epilepsy. The committee acknowledged that a reduction in seizure frequency or intensity (or obtaining seizure freedom) may decrease the probability of experiencing long-term complications or comorbidities associated with drug resistant epilepsy, thus resulting in cost savings for the NHS.

The committee highlighted there are potentially significant benefits for VNS. For example, when people with drug-resistant epilepsy are informed they are not eligible for resective epilepsy surgery this can have a severe negative psychological impact due to the prospect of limited treatment options being available. Therefore, VNS can provide hope for people's long-term prognosis of drug-refractory epilepsy and thus improve QoL.

The outcome used in the threshold calculations was a greater than fifty percent reduction in seizure frequency and the committee noted that people achieving this outcome – or seizure freedom – would likely observe a significant improvement in their QoL. The committee did however emphasise that any reduction in seizure frequency or intensity would highly likely improve a person's QoL. The committee also discussed that if people with depression experience an improvement in seizure frequency or intensity this also has the potential to significantly improve a person's QoL.

Overall, the committee concluded that VNS would be more expensive than continued treatment with ASMs, however these cost differences have the potential to be offset by QoL improvements observed for a drug-refectory population where all other treatment options have been exhausted.

The recommendations made are largely reflective of current practice and so are not expected to result in a significant resource impact. The committee also acknowledged that additional research is needed in this area and therefore made a research recommendation to assess the effectiveness of VNS in people with epilepsy, including people with learning disabilities as a subgroup.

1.1.11.4 Other factors the committee took into account

The committee agreed the guideline should cross refer to the interventional procedure guidance for VNS for children with refractory epilepsy (IPG50).

1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendations 8.3.1 – 8.3.2 and the research recommendation on the effectiveness of vagus nerve stimulation in epilepsy.

References

1. Aalbers MW, Klinkenberg S, Rijkers K, Verschuure P, Kessels A, Aldenkamp A et al. The effects of vagus nerve stimulation on pro- and anti-inflammatory cytokines in children with refractory epilepsy: an exploratory study. Neuroimmunomodulation. 2012; 19(6):352-358

2. Aihua L, Lu S, Liping L, Xiuru W, Hua L, Yuping W. A controlled trial of transcutaneous vagus nerve stimulation for the treatment of pharmacoresistant epilepsy. Epilepsy & Behavior. 2014; 39:105-110

3. Amar AP. Vagus nerve stimulation for the treatment of intractable epilepsy. Expert Review of Neurotherapeutics. 2007; 7(12):1763-1773

4. Amar AP, DeGiorgio CM, Tarver WB, Apuzzo ML. Long-term multicenter experience with vagus nerve stimulation for intractable partial seizures: results of the XE5 trial. Stereotactic and Functional Neurosurgery. 1999; 73(1-4):104-108

5. Amar AP, Heck CN, DeGiorgio CM, Apuzzo ML. Experience with vagus nerve stimulation for intractable epilepsy: some questions and answers. Neurologia Medico-Chirurgica. 1999; 39(7):489-495

6. Amar AP, Heck CN, Levy ML, Smith T, DeGiorgio CM, Oviedo S et al. An institutional experience with cervical vagus nerve trunk stimulation for medically refractory epilepsy: Rationale, technique, and outcome. Neurosurgery. 1998; 43(6):1265-1280

7. Bauer S, Baier H, Baumgartner C, Bohlmann K, Fauser S, Graf W et al. Transcutaneous Vagus Nerve Stimulation (tVNS) for treatment of drug-resistant epilepsy: a randomized, double-blind clinical trial (cMPsE02). Brain Stimulation. 2016; 9(3):356-363

8. Ben-Menachem E. Vagus-nerve stimulation for the treatment of epilepsy. Lancet Neurology. 2002; 1(8):477-482

9. Ben-Menachem E, Manon-Espaillat R, Ristanovic R, Wilder BJ, Stefan H, Mirza W et al. Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of effect on seizures. First International Vagus Nerve Stimulation Study Group. Epilepsia. 1994; 35(3):616-626

10. Bernstein AL, Hess T. Vagus nerve stimulation therapy for pharmacoresistant epilepsy: effect on health care utilization. Epilepsy & Behavior. 2007; 10(1):134-137

11. Boon P, Raedt R, de Herdt V, Wyckhuys T, Vonck K. Electrical stimulation for the treatment of epilepsy. Neurotherapeutics. 2009; 6(2):218-227

12. Boon P, Vonck K, D'Have M, O'Connor S, Vandekerckhove T, De Reuck J. Cost-benefit of vagus nerve stimulation for refractory epilepsy. Acta Neurologica Belgica. 1999; 99(4):275-280

13. Boon P, Vonck K, de Reuck J, Caemaert J. Vagus nerve stimulation for refractory epilepsy. Seizure. 2002; 11 (Suppl A):448-455

14. Boon P, Vonck K, Vandekerckhove T, De Reuck J, Calliauw L. Vagus nerve stimulation for refractory epilepsy. Neurosurgery Quarterly. 2001; 11(1):66-72

15. Broncel A, Blizniewska K, Talarowska M. How does vagus nerve stimulation (VNS) affect cognition? A review. Medical Science Technology. 2017; 58:67-72

16. Bryant J, Stein K. Vagus nerve stimulation in epilepsy. Southampton. (WIHRD) WIfHRaD, 1998. Available from: http://www.wihrd.soton.ac.uk

17. Bunch S, DeGiorgio CM, Krahl S, Britton J, Green P, Lancman M et al. Vagus nerve stimulation for epilepsy: is output current correlated with acute response? Acta Neurologica Scandinavica. 2007; 116(4):217-220

18. Chambers A, Bowen JM. Electrical stimulation for drug-resistant epilepsy: an evidence-based analysis. Ontario Health Technology Assessment Series. 2013; 13(18):1-37

19. Clark KB, Naritoku DK, Smith DC, Browning RA, Jensen RA. Enhanced recognition memory following vagus nerve stimulation in human subjects. Nature Neuroscience. 1999; 2(1):94-98

20. Clarke BM, Upton AR, Griffin H, Fitzpatrick D, DeNardis M. Chronic stimulation of the left vagus nerve: cognitive motor effects. Canadian Journal of Neurological Sciences. 1997; 24(3):226-229

21. Clarke BM, Upton AR, Griffin H, Fitzpatrick D, DeNardis M. Seizure control after stimulation of the vagus nerve: clinical outcome measures. Canadian Journal of Neurological Sciences. 1997; 24(3):222-225

22. Colicchio G, Policicchio D, Barbati G, Cesaroni E, Fuggetta F, Meglio M et al. Vagal nerve stimulation for drug-resistant epilepsies in different age, aetiology and duration. Child's Nervous System. 2010; 26(6):811-819

23. Cramer JA. Exploration of changes in health-related quality of life after 3 months of vagus nerve stimulation. Epilepsy & Behavior. 2001; 2(5):460-465

24. Crumrine PK. Vagal nerve stimulation in children. Seminars in Pediatric Neurology. 2000; 7(3):216-223

25. Cukiert A. Vagus nerve stimulation for epilepsy: An evidence-based approach. Progress in Neurological Surgery. 2015; 29:39-52

26. Dasheiff RM, Sandberg T, Thompson J, Arrambide S, E, Group ECS. Vagal nerve stimulation does not unkindle seizures. Journal of Clinical Neurophysiology. 2001; 18(1):68-74

27. de Kinderen RJ, Postulart D, Aldenkamp AP, Evers SM, Lambrechts DA, Louw AJ et al. Cost-effectiveness of the ketogenic diet and vagus nerve stimulation for the treatment of children with intractable epilepsy. Epilepsy Research. 2015; 110:119-131

28. DeGiorgio CM, Schachter SC, Handforth A, Salinsky M, Thompson J, Uthman B et al. Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures. Epilepsia. 2000; 41(9):1195-1200

29. DeGiorgio CM, Thompson J, Lewis P, Arrambide S, Naritoku D, Handforth A et al. Vagus nerve stimulation: analysis of device parameters in 154 patients during the long-term XE5 study. Epilepsia. 2001; 42(8):1017-1020

30. Dibue-Adjei M, Brigo F, Yamamoto T, Vonck K, Trinka E. Vagus nerve stimulation in refractory and super-refractory status epilepticus - A systematic review. Brain Stimulation. 2019; 12(5):1101-1110

31. Dodrill CB, Morris GL. Effects of vagal nerve stimulation on cognition and quality of life in epilepsy. Epilepsy & Behavior. 2001; 2(1):46-53

32. Elger G, Hoppe C, Falkai P, Rush AJ, Elger CE. Vagus nerve stimulation is associated with mood improvements in epilepsy patients. Epilepsy Research. 2000; 42(2-3):203-210

33. Elliott RE, Morsi A, Kalhorn SP, Marcus J, Sellin J, Kang M et al. Vagus nerve stimulation in 436 consecutive patients with treatment-resistant epilepsy: long-term outcomes and predictors of response. Epilepsy & Behavior. 2011; 20(1):57-63

34. Englot DJ, Chang EF, Auguste KI. Vagus nerve stimulation for epilepsy: A meta-analysis of efficacy and predictors of response - A review. Journal of Neurosurgery. 2011; 115(6):1248-1255

35. Englot DJ, Rolston JD, Wright CW, Hassnain KH, Chang EF. Rates and predictors of seizure freedom with vagus nerve stimulation for intractable epilepsy. Neurosurgery. 2016; 79(3):345-353

36. Faught E. Treatment of refractory primary generalized epilepsy. Reviews in Neurological Diseases. 2004; 1 (Suppl 1):S34-43

37. Forbes R. Cost-utility of vagus nerve stimulation (VNS) therapy for medically refractory epilepsy--an update. Seizure. 2008; 17(4):387-388

38. Forbes RB, MacDonald S, Eljamel S, Roberts RC. Cost-utility analysis of vagus nerve stimulators for adults with medically refractory epilepsy. Seizure. 2003; 12(5):249-256

39. George R, Salinsky M, Kuzniecky R, Rosenfeld W, Bergen D, Tarver WB et al. Vagus nerve stimulation for treatment of partial seizures: 3. Long-term follow-up on first 67 patients exiting a controlled study. First International Vagus Nerve Stimulation Study Group. Epilepsia. 1994; 35(3):637-643

40. Ghani S, Vilensky J, Turner B, Tubbs RS, Loukas M. Meta-analysis of vagus nerve stimulation treatment for epilepsy: correlation between device setting parameters and acute response. Childs Nervous System. 2015; 31(12):2291-2304

41. Handforth A, DeGiorgio CM, Schachter SC, Uthman BM, Naritoku DK, Tecoma ES et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology. 1998; 51(1):48-55

42. He W, Jing X, Wang X, Rong P, Li L, Shi H et al. Transcutaneous auricular vagus nerve stimulation as a complementary therapy for pediatric epilepsy: a pilot trial. Epilepsy & Behavior. 2013; 28(3):343-346

43. He W, Wang XY, Zhou L, Li ZM, Jing XH, Lv ZL et al. Transcutaneous auricular vagus nerve stimulation for pediatric epilepsy: study protocol for a randomized controlled trial. Trials. 2015; 16:371

44. Henry, T R, Bakay, R A, Votaw, J R et al. Brain blood flow alterations induced by therapeutic vagus nerve stimulation in partial epilepsy: i. Acute effects at high and low levels of stimulation. Epilepsia. 1998; 39(9):983-990

45. Holder LK, Wernicke JF, Tarver WB. Treatment of refractory partial seizures: preliminary results of a controlled study. Pacing and Clinical Electrophysiology. 1992; 15(10 Pt 2):1557-1571

46. Hsiang JN, Wong LK, Kay R, Poon WS. Vagus nerve stimulation for seizure control: Local experience. Journal of Clinical Neuroscience. 1998; 5(3):294-297

47. Ji T, Yang Z, Liu Q, Liao J, Yin F, Chen Y et al. Vagus nerve stimulation for pediatric patients with intractable epilepsy between 3 and 6 years of age: study protocol for a double-blind, randomized control trial. Trials. 2019; 20:44

48. Kersing W, Dejonckere PH, Van der Aa HE, Buschman HPJ. Laryngeal and vocal changes during vagus nerve stimulation in epileptic patients. Journal of Voice. 2002; 16(2):251-257

49. Klinkenberg S, Aalbers MW, Vles JS, Cornips EM, Rijkers K, Leenen L et al. Vagus nerve stimulation in children with intractable epilepsy: a randomized controlled trial. Developmental Medicine and Child Neurology. 2012; 54(9):855-861

50. Klinkenberg S, van den Borne CJ, Aalbers MW, Verschuure P, Kessels AG, Leenen L et al. The effects of vagus nerve stimulation on tryptophan metabolites in children with intractable epilepsy. Epilepsy & Behavior. 2014; 37:133-138

51. Klinkenberg S, van den Bosch CN, Majoie HJ, Aalbers MW, Leenen L, Hendriksen J et al. Behavioural and cognitive effects during vagus nerve stimulation in children with intractable epilepsy - a randomized controlled trial. European Journal of Paediatric Neurology. 2013; 17(1):82-90

52. Kopciuch D, Barciszewska AM, Flicinski J, Paczkowska A, Winczewska-Wiktor A, Jankowski R et al. Economic and clinical evaluation of vagus nerve stimulation therapy. Acta Neurologica Scandinavica. 2019; 140(4):244-251

53. Kopciuch D, Barciszewska AM, Flicinski J, Zaprutko T, Kus K, Steinborn B et al. Analysis of pharmacotherapy regimen and costs in patients with drug-resistant epilepsy following vagus nerve stimulation therapy: a single-center study (Poland). Acta Neurologica Belgica. 2020; 120(1):115-122

54. Kwan H, Garzoni L, Liu HL, Cao M, Desrochers A, Fecteau G et al. Vagus nerve stimulation for treatment of inflammation: Systematic review of animal models and clinical studies. Bioelectronic Medicine. 2016; 3:1-6

55. Labar D. Vagus nerve stimulation for epilepsy. Clinical Neuroscience Research. 2004; 4(1-2):81-87

56. Labar D. Vagus nerve stimulation for intractable epilepsy in children. Developmental Medicine and Child Neurology. 2000; 42(7):496-499

57. Landy HJ, Ramsay RE, Slater J, Casiano RR, Morgan R. Vagus nerve stimulation for complex partial seizures: surgical technique, safety, and efficacy. Journal of Neurosurgery. 1993; 78(1):26-31

58. Marras CE, Chiesa V, De Benedictis A, Franzini A, Rizzi M, Villani F et al. Vagus nerve stimulation in refractory epilepsy: new indications and outcome assessment. Epilepsy & Behavior. 2013; 28(3):374-378

59. Marson AG, Maguire M, Ramaratnam S. Epilepsy. Clinical Evidence. 2012; 02:1201

60. McGlone J, Valdivia I, Penner M, Williams J, Sadler RM, Clarke DB. Quality of life and memory after vagus nerve stimulator implantation for epilepsy. Canadian Journal of Neurological Sciences. 2008; 35(3):287-296

61. Michael JE, Wegener K, Barnes DW. Vagus nerve stimulation for intractable seizures: one year follow-up. Journal of Neuroscience Nursing. 1993; 25(6):362-366

62. Milby AH, Halpern CH, Baltuch GH. Vagus nerve stimulation in the treatment of refractory epilepsy. Neurotherapeutics. 2009; 6(2):228-237

63. Murphy JV. Left vagal nerve stimulation in children with medically refractory epilepsy. Journal of Pediatrics. 1999; 134(5):563-566

64. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [updated October 2020]. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

65. National Institute for Health and Clinical Excellence. Vagus nerve stimulation for refractory epilepsy in children. NICE interventional procedure guidance 50. London. National Institute for Health and Clinical Excellence (NICE), 2004. Available from: http://www.nice.org.uk/IPG50

66. Panebianco M, Rigby A, Weston J, Marson AG. Vagus nerve stimulation for partial seizures. Cochrane Database of Systematic Reviews 2015, Issue 4. Art. No.: CD002896. DOI: 10.1002/14651858.CD002896.pub2.

67. Patwardhan RV, Stong B, Bebin EM, Mathisen J, Grabb PA. Efficacy of vagal nerve stimulation in children with medically refractory epilepsy. Neurosurgery. 2000; 47(6):1353-1358

68. Pizzanelli C, Galli R, Giorgi FS, Iudice A, Bonanni E, Pelliccia V et al. Vagus nerve stimulation as a treatment for refractory epilepsy: A 15-year experience in an Italian Tertiary - Care epilepsy center. Letters in Drug Design and Discovery. 2011; 8(4):321-329

69. Privitera MD, Welty TE, Ficker DM, Welge J. Vagus nerve stimulation for partial seizures. Cochrane Database of Systematic Reviews 2002, Issue 1. Art. No.: CD002896. DOI: 10.1002/14651858.CD002896.

70. Ramsay RE, Uthman BM, Augustinsson LE, Upton AR, Naritoku D, Willis J et al. Vagus nerve stimulation for treatment of partial seizures: 2. Safety, side effects, and tolerability. First International Vagus Nerve Stimulation Study Group. Epilepsia. 1994; 35(3):627-636

71. Redgrave J, Day D, Leung H, Laud PJ, Ali A, Lindert R et al. Safety and tolerability of transcutaneous vagus nerve stimulation in humans; a systematic review. Brain Stimulation. 2018; 11(6):1225-1238

72. Rong P, Liu A, Zhang J, Wang Y, He W, Yang A et al. Transcutaneous vagus nerve stimulation for refractory epilepsy: a randomized controlled trial. Clinical Science. 2014; 10.1042/CS20130518

73. Rong P, Liu A, Zhang J, Wang Y, Yang A, Li L et al. An alternative therapy for drug-resistant epilepsy: transcutaneous auricular vagus nerve stimulation. Chinese Medical Journal. 2014; 127(2):300-304

74. Ryvlin P, Gilliam FG, Nguyen DK, Colicchio G, Iudice A, Tinuper P et al. Erratum: The long-term effect of vagus nerve stimulation on quality of life in patients with pharmacoresistant focal epilepsy: The PuLsE (Open Prospective Randomized Long-term Effectiveness) trial (Epilepsia (2014) 55 (893-900)). Epilepsia. 2014; 55(9):1476

75. Ryvlin P, Gilliam FG, Nguyen DK, Colicchio G, Iudice A, Tinuper P et al. Erratum: The long-term effect of vagus nerve stimulation on quality of life in patients with pharmacoresistant focal epilepsy: The PuLsE (Open Prospective Randomized Long-term Effectiveness) trial (Epilepsia (2014) 55(893-900)). Epilepsia. 2015; 56(6):983

76. Ryvlin P, Gilliam FG, Nguyen DK, Colicchio G, Iudice A, Tinuper P et al. The long-term effect of vagus nerve stimulation on quality of life in patients with pharmacoresistant focal epilepsy: the PuLsE (Open Prospective Randomized Long-term Effectiveness) trial. Epilepsia. 2014; 55(6):893-900

77. Salinsky MC. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. Neurology. 1995; 45(2):224-230

78. Salinsky MC. Vagus nerve stimulation as treatment for epileptic seizures. Current Treatment Options in Neurology. 2003; 5(2):111-120

79. Salinsky MC, Uthman BM, Ristanovic RK, Wernicke JF, Tarver WB. Vagus nerve stimulation for the treatment of medically intractable seizures. Results of a 1-year open-extension trial. Vagus Nerve Stimulation Study Group. Archives of Neurology. 1996; 53(11):1176-1180

80. Scherrmann J, Hoppe C, Kral T, Schramm J, Elger CE. Vagus nerve stimulation: clinical experience in a large patient series. Journal of Clinical Neurophysiology. 2001; 18(5):408-414

81. Selner AN, Rosinski CL, Chiu RG, Rosenberg D, Chaker AN, Drammeh H et al. Vagal nerve stimulation for epilepsy in adults: A database risk analysis and review of the literature. World Neurosurgery. 2019; 121:e947-e953

82. Sirven JI, Sperling M, Naritoku D, Schachter S, Labar D, Holmes M et al. Vagus nerve stimulation therapy for epilepsy in older adults. Neurology. 2000; 54(5):1179-1182

83. Soleman J, Stein M, Knorr C, Datta AN, Constantini S, Fried I et al. Improved quality of life and cognition after early vagal nerve stimulator implantation in children. Epilepsy & Behavior. 2018; 88:139-145

84. Sourbron J, Klinkenberg S, Kessels A, Schelhaas HJ, Lagae L, Majoie M. Vagus nerve stimulation in children: A focus on intellectual disability. European Journal of Paediatric Neurology. 2017; 21(3):427-440

85. Stefan H, Kreiselmeyer G, Kerling F, Kurzbuch K, Rauch C, Heers M et al. Transcutaneous vagus nerve stimulation (t-VNS) in pharmacoresistant epilepsies: a proof of concept trial. Epilepsia. 2012; 53(7):e115-118

86. Tecoma ES, Iragui VJ. Vagus nerve stimulation use and effect in epilepsy: what have we learned? Epilepsy & Behavior. 2006; 8(1):127-136

87. Uthman BM. Vagus nerve stimulation for seizures. Archives of Medical Research. 2000; 31(3):300-303

88. Wheless JW, Baumgartner J. Vagus nerve stimulation therapy. Drugs of Today. 2004; 40(6):501-515

89. Wiebe S, Jette N. Randomized trials and collaborative research in epilepsy surgery: future directions. Canadian Journal of Neurological Sciences. 2006; 33(4):365-371

90. Wilder BJ, Uthman BM, Hammond EJ. Vagal stimulation for control of complex partial seizures in medically refractory epileptic patients. Pacing and Clinical Electrophysiology. 1991; 14(1):108-115

91. Zeiler FA, Zeiler KJ, Teitelbaum J, Gillman LM, West M. VNS for refractory status epilepticus. Epilepsy Research. 2015; 112:100-113

Appendices

Appendix A: Review protocols

Table 9: Review protocol: Vagus nerve stimulation

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	Review protocol for vagus nerve stimulation. Question number: 5.3
2.	Review question	What is the effectiveness of vagus nerve stimulation in epilepsy?
3.	Objective	The aim of the review is to determine the effectiveness of vagus nerve stimulation in people with pharmacoresistant epilepsy Up to 70% of people with epilepsy will respond to 1st or 2nd line drug therapy. A surgical procedure such as vagus nerve stimulation would only be considered once these options have been trialled. A pacemaker device is implanted under the skin and stimulating electrodes generate electrical signals from the device to the left vagus nerve. The device can be programmed to vary the frequency, intensity and duration of the signal. Vagus nerve stimulation has been around for quite some time, but only over the past couple of years has there been a real push in increasing the settings of the device. This clearly depletes the battery at a much faster rate, meaning that the patients need battery replacements more often and the new batteries are becoming increasingly expensive. It would be really important to identify if the outcomes are really better with increased stimulation. This will also represent a new key point with respect to the previous guideline
4.	Searches	The following databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE Searches will be restricted by: English language The searches may be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion if relevant. The full search strategies for MEDLINE database will be published in the final review.

ID	Field	Content
5.	Condition or domain being studied	Pharmacoresistant epilepsy Epilepsy is a common treatable condition, characterised by recurrent involuntary brain activity that manifests as seizures. Although the majority of people have a good response to antiepileptic drugs and become seizure free, approximately 30% continue to have seizures despite taking multiple antiepileptic drugs (pharmacoresistant epilepsy).
6.	Population	Inclusion: Children, young people and adults with confirmed pharmacoresistant epilepsy Strata: evidence in people with learning disabilities will be presented separately from evidence in people without learning disabilities (to be analysed separately) Exclusion: New-born babies (under 28 days) with acute symptomatic seizures.
7.	Intervention/Exposure/Test	High frequency vagus nerve stimulation Low frequency vagus nerve stimulation Auto stimulation (rapid cycling) and SenTiva device
8.	Comparator/Reference standard/Confounding factors	Sham or usual care One vagus nerve stimulation method vs different vagus nerve stimulation method
9.	Types of study to be included	Randomised controlled trials (RCTs) Systematic reviews of RCTs If no RCTs are found for a particular intervention, prospective observational comparative studies will be considered only if they adjust for the key confounders of age of epilepsy onset, classification (focal, generalised, or epilepsy syndrome), earlier invasive epilepsy surgery, number of AEDs tried prior to intervention, AED changes recorded during intervention reporting, gender, mental health and learning disability For a systematic review to be included it must be conducted to the same methodological standard as NICE guideline reviews. If sufficient details are not provided to include a relevant systematic review, the review will only be used for citation searching.
10.	Other exclusion criteria	Exclusions: Non-English language publications Conference abstracts
11.	Context	Previous recommendations:

ID	Field	Content
		Vagus nerve stimulation is indicated for use as an adjunctive therapy in reducing the frequency of seizures in adults who are refractory to antiepileptic medication but who are not suitable for respective surgery. This includes adults whose epileptic disorder is dominated by partial seizures (with or without secondary generalisation) or generalised seizures. Vagus nerve stimulation is indicated for use as an adjunctive therapy in reducing the frequency of seizures in children who are refractory to antiepileptic medication but who are not suitable for respective surgery. This includes children whose epileptic disorder is dominated by partial seizures (with or without secondary generalisation) or generalised seizures.

ID	Field	Content
12.	Primary outcomes (critical outcomes)	mortality at short-term follow-up of 12 months and longer-term follow-up of up to 60 months seizure freedom (100% reduction in seizure frequency) at short-term follow-up of 12 months and longer-term follow-up of up to 60 months seizure frequency (50% or greater reduction in seizure frequency) at short-term follow-up of 12 months and longer-term follow-up of up to 60 months quality of life (measured with a validated scale) at short-term follow-up of 12 months and longer-term follow-up of 60 months healthcare resource use social functioning (measures of adaptive functioning or adaptive behaviour using a validated scale) short-term follow-up of 12 months and longer-term follow-up of up to 60 months cognitive outcomes (including neuropsychological measures of global cognitive functioning, executive functioning and memory using a validated scale) short-term follow-up of 12 months and longer-term follow-up of up to 60 months in children and young people: neurodevelopmental outcomes (behavioural and emotional outcomes measured with a validated scale) short-term follow-up of 12 months and longer-term follow-up of up to 60 months adverse events (analysed separately): lead fracture infection hoarse voice cardiac difficulties device removal
13.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above.

ID	Field	Content
14.	Risk of bias (quality) assessment	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) Randomised Controlled Trial: Cochrane RoB (2.0) Nonrandomised study, including cohort studies: Cochrane ROBINS-I 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: papers were included /excluded appropriately a sample of the data extractions correct methods are used to synthesise data a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
115	Strategy for data synthesis	EndNote will be used for reference management, sifting, citations and bibliographies. EviBASE will be used for data extraction and quality assessment for clinical studies. MS Excel will be used for data extraction and critical appraisal for health economic studies. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). GRADEpro will be used to assess the quality of evidence for each outcome
16.	Analysis of sub-groups	Groups to be considered from the equality impact assessment: children and young people girls and women of who are able to get pregnant (including those who are pregnant and breastfeeding) older people people with learning disabilities Statistically heterogeneity will be assessed by visually examining the forest plots and by calculating the I2 inconsistency statistic (with an I2 value of more than 50% indicating considerable heterogeneity). In the event of heterogeneity, subgroup analysis will be undertaken based on the following possible modifiers of treatment effect:

ID	Field	Content			
		children, young people and adults type of epilepsy (generalised, focal, epilepsy syndrome) type of vagus nerve stimulation method (for example higher intensity older methods vs newer high intensity methods)			
17.	Type and method of review	☒	Intervention		
		☐	Diagnostic		
		☐	Prognostic		
		☐	Qualitative		
		☐	Epidemiologic		
		☐	Service Delivery		
		☐	Other (please specify)		
18.	Language	English			
19.	Country	England			
20.	Anticipated or actual start date	[For the purposes of PROSPERO, the date of commencement for the systematic review can be defined as any point after completion of a protocol but before formal screening of the identified studies against the eligibility criteria begins. A protocol can be deemed complete after sign-off by the NICE team with responsibility for quality assurance.]			
21.	Anticipated completion date	[Give the date by which the guideline is expected to be published. This field may be edited at any time. All edits will appear in the record audit trail. A brief explanation of the reason for changes should be given in the Revision Notes facility.]			
22.	Stage of review at time of this submission	Review stage		Started	Completed
		Preliminary searches		☑	☐
		Piloting of the study selection process		☐	☐
		Formal screening of search results against eligibility criteria		☐	☐
		Data extraction		☐	☐

ID	Field	Content		
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
23.	Named contact	5a. Named contact National Guideline Centre Angela Cooper angela.cooper@rcplondon.ac.uk 5b Named contact e-mail [Guideline email]@nice.org.uk [Developer to check with Guideline Coordinator for email address] 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
24.	Review team members	From the National Guideline Centre: Gill Ritchie, Guideline Lead Angela Cooper, Senior Research Fellow Jacqui Real, Senior Research Fellow Rafina Yarde, Systematic reviewer Margaret Constanti, Senior Health economist Joseph Runicles, Information specialist		
25.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		

ID	Field	Content	
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].	
28.	Other registration details		
29.	Reference/URL for published protocol	Give the citation and link for the published protocol, if there is one.	
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
31.	Keywords	Epilepsy Vagus nerve stimulation	
32.	Details of existing review of same topic by same authors		
33.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
34.	Additional information		
35.	Details of final publication	www.nice.org.uk	

Table 10: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2004, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2004 that were included in the previous guideline(s) will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[64] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations', then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations', then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies.

	Setting: • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2004 or later (including any such studies included in the previous guideline(s)) but that depend on unit costs and resource data entirely or predominantly from before 2004 will be rated as 'Not applicable'. • Studies published before 2004 (including any such studies included in the previous guideline(s)) will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

This literature search strategy was used for the following review:

- What is the effectiveness of vagus nerve stimulation in epilepsy?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[64]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 11: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 13 May 2021	Randomised controlled trials

Database	Dates searched	Search filter used
		Systematic review studies Observational studies Exclusions
Embase (OVID)	1974 – 13 May 2021	Randomised controlled trials Systematic review studies Observational studies Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2021 Issue 5 of 12 CENTRAL to 2021 Issue 5 of 12	None

Medline (Ovid) search terms

1.	exp epilepsy/
2.	seizures/
3.	exp status epilepticus/
4.	seizures, febrile/
5.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Vagus Nerve/ or vagus nerve stimulation/
28.	((vagus or vagal or electric*) adj3 (stimul* or therap* or treatment*)).ti,ab.
29.	(VNS or pulse generator or LivaNova or Aspire* or SenTiva or autostim*).ti,ab.
30.	or/27-29

31.	randomized controlled trial.pt.
32.	controlled clinical trial.pt.
33.	randomi#ed.ti,ab.
34.	placebo.ab.
35.	randomly.ti,ab.
36.	Clinical Trials as topic.sh.
37.	trial.ti.
38.	or/31-37
39.	Meta-Analysis/
40.	exp Meta-Analysis as Topic/
41.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
42.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
43.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
44.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
45.	(search* adj4 literature).ab.
46.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
47.	cochrane.jw.
48.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
49.	or/39-48
50.	Epidemiologic studies/
51.	Observational study/
52.	exp Cohort studies/
53.	(cohort adj (study or studies or analys* or data)).ti,ab.
54.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
55.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
56.	Controlled Before-After Studies/
57.	Historically Controlled Study/
58.	Interrupted Time Series Analysis/
59.	(before adj2 after adj2 (study or studies or data)).ti,ab.
60.	exp case control studies/
61.	case control*.ti,ab.
62.	Cross-sectional studies/
63.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
64.	or/50-63
65.	26 and 30 and (38 or 49 or 64)

Embase (Ovid) search terms

1.	exp epilepsy/
2.	seizure/
3.	epileptic state/
4.	febrile convulsion/
5.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.

6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	Vagus Nerve/ or vagus nerve stimulation/
26.	((vagus or vagal or electric*) adj3 (stimul* or therap* or treatment*)).ti,ab.
27.	(VNS or pulse generator or LivaNova or Aspire* or SenTiva or autostim*).ti,ab.
28.	or/25-27
29.	random*.ti,ab.
30.	factorial*.ti,ab.
31.	(crossover* or cross over*).ti,ab.
32.	((doubl* or singl*) adj blind*).ti,ab.
33.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
34.	crossover procedure/
35.	single blind procedure/
36.	randomized controlled trial/
37.	double blind procedure/
38.	or/29-37
39.	systematic review/
40.	meta-analysis/
41.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
42.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
43.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
44.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
45.	(search* adj4 literature).ab.
46.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
47.	cochrane.jw.
48.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
49.	or/39-48
50.	Clinical study/

51.	Observational study/
52.	family study/
53.	longitudinal study/
54.	retrospective study/
55.	prospective study/
56.	cohort analysis/
57.	follow-up/
58.	cohort*.ti,ab.
59.	57 and 58
60.	(cohort adj (study or studies or analys* or data)).ti,ab.
61.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
62.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
63.	(before adj2 after adj2 (study or studies or data)).ti,ab.
64.	exp case control study/
65.	case control*.ti,ab.
66.	cross-sectional study/
67.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
68.	or/50-56,59-67
69.	24 and 28 and (38 or 49 or 68)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Epilepsy] explode all trees
#2.	MeSH descriptor: [Seizures] explode all trees
#3.	MeSH descriptor: [Status Epilepticus] explode all trees
#4.	MeSH descriptor: [Seizures, Febrile] explode all trees
#5.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome):ti,ab
#6.	(or #1-#5)
#7.	MeSH descriptor: [Vagus Nerve] explode all trees
#8.	MeSH descriptor: [Vagus Nerve Stimulation] explode all trees
#9.	((vagus or vagal or electric*) near/3 (stimul* or therap* or treatment*)):ti,ab
#10.	(VNS or pulse generator or LivaNova or Aspire* or SenTiva or autostim*):ti,ab
#11.	(or #7-#10)
#12.	#6 and #11

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to an Epilepsies population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics and quality of life studies.

Table 12: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	Health Economics 1 January 2014 – 13 May 2021 Quality of Life 1946 – 13 May 2021	Health economics studies Quality of life studies Exclusions
Embase	Health Economics 1 January 2014 – 13 May 2021 Quality of Life 1974 – 13 May 2021	Health economics studies Quality of life studies Exclusions
Centre for Research and Dissemination (CRD)	HTA - Inception – 13 May 2021 NHSEED - Inception to 31 March 2015	None

Medline (Ovid) search terms

1.	exp epilepsy/
2.	seizures/
3.	exp status epilepticus/
4.	seizures, febrile/
5.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/

30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	quality-adjusted life years/
45.	sickness impact profile/
46.	(quality adj2 (wellbeing or well being)).ti,ab.
47.	sickness impact profile.ti,ab.
48.	disability adjusted life.ti,ab.
49.	(qal* or qtime* or qwb* or daly*).ti,ab.
50.	(euroqol* or eq5d* or eq 5*).ti,ab.
51.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
52.	(hui or hui1 or hui2 or hui3).ti,ab.
53.	(health* year* equivalent* or hye or hyes).ti,ab.
54.	discrete choice*.ti,ab.
55.	rosser.ti,ab.
56.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
57.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
58.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
59.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
60.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
61.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
62.	or/44-61
63.	26 and (43 or 62)

Embase (Ovid) search terms

1.	exp *epilepsy/
2.	*landau kleffner syndrome/
3.	exp *seizure/
4.	"seizure, epilepsy and convulsion"/
5.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.

9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	6 not 22
24.	limit 23 to English language
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	quality adjusted life year/
40.	sickness impact profile/
41.	(quality adj2 (wellbeing or well being)).ti,ab.
42.	sickness impact profile.ti,ab.
43.	disability adjusted life.ti,ab.
44.	(qal* or qtime* or qwb* or daly*).ti,ab.
45.	(euroqol* or eq5d* or eq 5*).ti,ab.
46.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
47.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
48.	(hui or hui1 or hui2 or hui3).ti,ab.
49.	(health* year* equivalent* or hye or hyes).ti,ab.
50.	discrete choice*.ti,ab.
51.	rosser.ti,ab.
52.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
53.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
54.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.

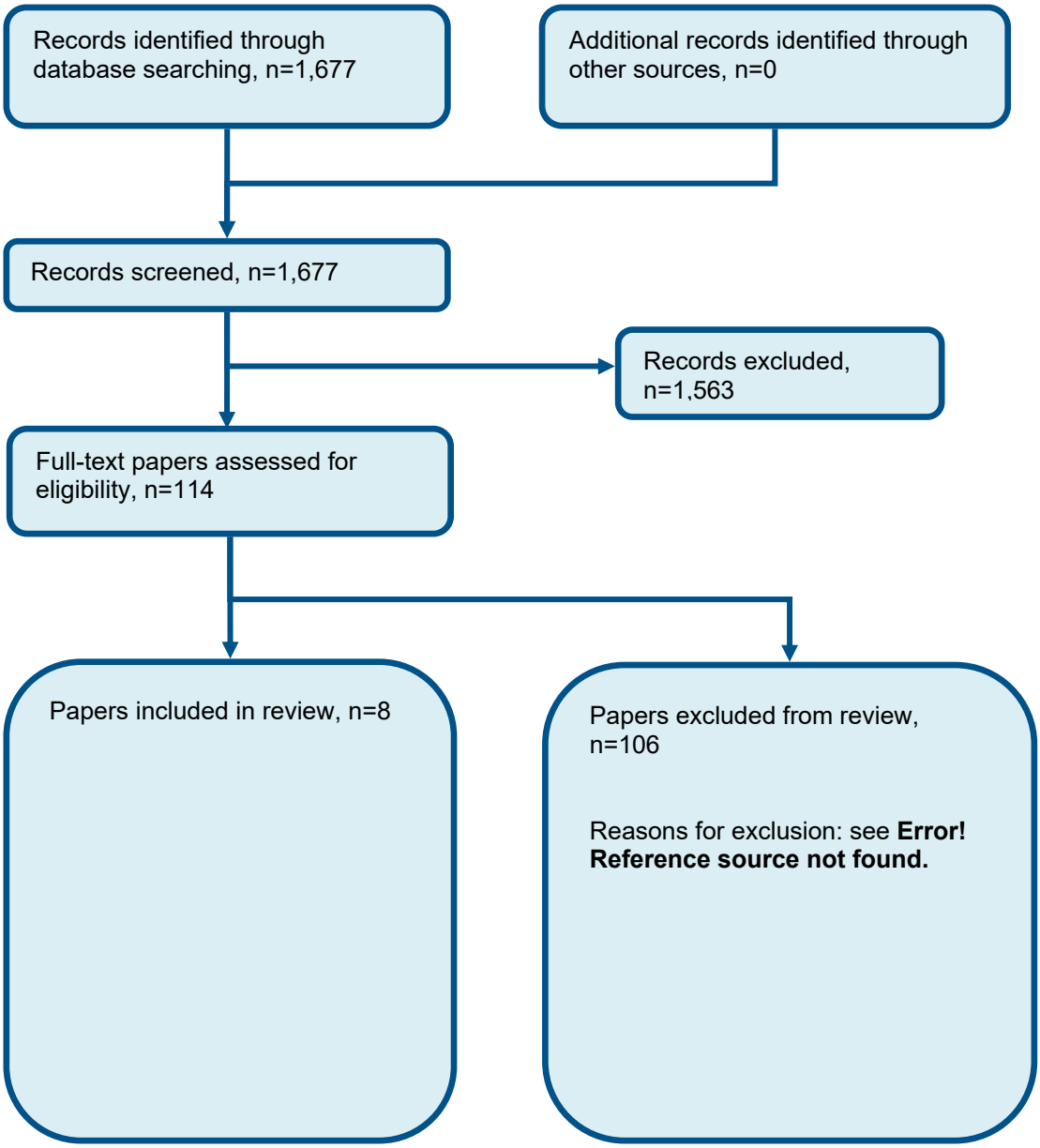
55.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
56.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
57.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
58.	or/39-57
59.	24 and (38 or 58)

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Epilepsy EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Seizures EXPLODE ALL TREES
#3.	MeSH DESCRIPTOR Status Epilepticus EXPLODE ALL TREES
#4.	MeSH DESCRIPTOR Seizures, Febrile EXPLODE ALL TREES
#5.	((dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome))
#6.	#1 OR #2 OR #3 OR #4 OR #5

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of vagus nerve stimulation



Appendix D: Clinical evidence tables

Study	**Bauer 2016[7]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=76)
Countries and setting	Conducted in Germany
Line of therapy	1st line
Duration of study	Intervention + follow up: 20 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Children, young people and adults with confirmed pharmacoresistant epilepsy
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients between 18 and 65 years of age were eligible for this study if they suffered from epilepsy with focal and/or generalised seizures, had ≥3 seizures per month and not more than 21 consecutive seizure free days. Seizure frequency was assessed retrospectively prior to screening and prospectively during the baseline period. Patients had to be on a stable regimen of ≤3 antiepileptic drugs (AEDs) for at least 5 weeks prior to study enrolment. This AED regimen had to be maintained throughout the study.
Exclusion criteria	Patients with more than one episode of status epilepticus within 6 months prior to study enrolment, current or prior treatment with invasive VNS or deep brain stimulation, prior ablative epilepsy surgery, history of non-epileptic seizures, major psychiatric disorders, deteriorating neurological or medical conditions and/or relevant cardiac diseases were excluded.
Age, gender and ethnicity	Age - Mean (SD): 38.8 (12.5). Gender (M:F): 45 female, 31 male. Ethnicity: Not stated.
Further population details	1. Children and young people: 2. Girls and women of who are able to get pregnant (including those who are pregnant and breastfeeding): 3. Older people: Older people (Mean age 38). 4. People with learning disabilities: 5. Type of epilepsy:

Study	Bauer 2016[7]
Indirectness of population	No indirectness
Interventions	(n=37) Intervention 1: High frequency vagus nerve stimulation. High level transcutaneous vagus nerve stimulation (t-VNS) - active treatment, 25 Hz stimulation frequency, 250µs pulse width, 30s on/30s off. For 4 hours daily for a period of 20 weeks. Patients received 180,000 stimuli per day.. Duration 20 weeks. Concurrent medication/care: Stimulation was performed using the CE certified t-VNS device NEMOS. The patients' current anticonvulsive drug treatment was not changed during the study. Indirectness: No indirectness Further details: 1. Type of vagus nerve stimulation method: (n=39) Intervention 2: Low frequency vagus nerve stimulation. Low level treatment - active control, 1 Hz stimulation frequency, 250µs pulse width, 30s on/30s off, for 4 hours daily for a period of 20 weeks. Duration 20 weeks. Concurrent medication/care: Stimulation was performed using the CE certified t-VNS device NEMOS. The patients' current anticonvulsive drug treatment was not changed during the study.. Indirectness: No indirectness Further details: 1. Type of vagus nerve stimulation method:
Funding	Funding not stated (N/A)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HIGH FREQUENCY VAGUS NERVE STIMULATION versus LOW FREQUENCY VAGUS NERVE STIMULATION Protocol outcome 1: Adverse events (lead fracture, infection, hoarse voice, cardiac difficulties, device removal) at N/A - Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Cardiac difficulties - palpitations at within weeks at 20 weeks; Group 1: 0/37, Group 2: 1/39 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10, Reason: Other, no compliance with study requirements, withdrawal of consent, condition described in exclusion criteria, further participation puts patient at risk ; Group 2 Number missing: 8, Reason: Other, no compliance with study requirements, withdrawal of consent or death	
Protocol outcomes not reported by the study	Quality of life at 12 months at 12 months; Quality of life at 60 months at 60 months; Mortality at 12 months at 12 months; Mortality at 60 months at 60 months; Seizure freedom (100% reduction in seizure frequency) at

Study	Bauer 2016[7]
	12 months at 12 months; Seizure freedom (100% reduction in seizure frequency) at 60 months at 60 months; Seizure frequency (50% or greater reduction in seizure frequency) at 12 months at 12 months; Seizure frequency (50% or greater reduction in seizure frequency) at 60 months at 60 months; Healthcare resource use at N/A; Social functioning (measures of adaptive functioning or adaptive behaviour using a validated scale) at 12 months at 12 months; Social functioning (measures of adaptive functioning or adaptive behaviour using a validated scale) at 60 months at 60 months; Cognitive outcomes (including neuropsychological measures of global cognitive functioning, executive functioning and memory using a validated scale) at 12 months at 12 months; Cognitive outcomes (including neuropsychological measures of global cognitive functioning, executive functioning and memory using a validated scale) at 60 months at 60 months; In children and young people: neurodevelopmental outcomes (behavioural and emotional outcomes measured with a validated scale) at 12 months at 12 months; In children and young people: neurodevelopmental outcomes (behavioural and emotional outcomes measured with a validated scale) at 60 months at 60 months

Study	Handforth 1998[41]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=198)
Countries and setting	Conducted in USA
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Children, young people and adults with confirmed pharmacoresistant epilepsy
Subgroup analysis within study	Not applicable
Inclusion criteria	Eligible if they had at least 6 partial onset seizures involving alteration of consciousness (complex partial or secondarily generalized convulsions) over 30 days, with no more than 21 days between seizure. Patients

Study	Handforth 1998[41]
	could also have other seizure types. Patients were required to submit accurate seizure counts, with or without the assistance of a caregiver, be age 12 to 65 years, use acceptable contraception if female and fertile, and take one to three marketed antiepileptic drugs on a stable regimen for at least 1 month or 5 half-lives plus 2 weeks (whichever was longer) before study entry.
Exclusion criteria	Patients were excluded for deteriorating neurologic or medical conditions, pregnancy, cardiac or pulmonary disease, active peptic ulcer, history of non-epileptic seizures, more than one episode of status epilepticus in the previous 12 months, prior cervical vagotomy, inability to give proper consent, prior vagus nerve stimulation, prior brain stimulation, resective epilepsy surgery, or inability to perform pulmonary function tests or comply with clinic visits.
Age, gender and ethnicity	Age - Mean (SD): Low group - 34.2 (10.1), High group - 32.1 (10.8). Gender (M:F): 93 male, 105 female. Ethnicity: 171 white, 17 Hispanic, 10 other
Further population details	1. Children and young people: 2. Girls and women of who are able to get pregnant (including those who are pregnant and breastfeeding): 3. Older people: Older people 4. People with learning disabilities: 5. Type of epilepsy:
Indirectness of population	No indirectness
Interventions	(n=95) Intervention 1: High frequency vagus nerve stimulation. High stimulation group - received stimulation through stimulation thought from previous studies most effective, with on/off cycles of 30 seconds every 5 minutes, each on period consisting of 500μs duration pulses at 30Hz frequency. On initiation, the current was increased over 24 hours by a designated unblinded programmer at each site, from zero to a level perceived by the patient, yet tolerated. At a subsequent visit 2 weeks later and at three more visits over 12 to 16 weeks, the current could be increased as tolerated but could not exceed 3.5mA. Patients could also manually activate the device using a handheld magnet to produce a 30 second stimulation on period in an attempt to abort a seizure. Duration 3 months. Concurrent medication/care: Study was divided into baseline and treatment phases. Patients kept daily seizure records and reported adverse symptoms and medications. Antiepileptic drugs were not changed, except as necessary to maintain appropriate concentrations or in response to apparent drug toxicity. Indirectness: No indirectness Further details: 1. Type of vagus nerve stimulation method: (n=103) Intervention 2: Low frequency vagus nerve stimulation. Low frequency group - received stimulation believed to be less effective and thus represented an active control group. Patients received stimulation on/off cycles of 30 seconds every 3 hours, with each on cycle consisting of 130μs duration pulses at 1 Hz

Study	Handforth 1998[41]
	frequency. On initiation of stimulation at visit 5, the current was increased to the point of patient perception; on subsequent visits the device was interrogated as with high stimulation patients, but the current was not increased. Although patients could attempt to abort seizures with the magnet, the device was programmed so that the magnet did not activate the device. Duration 3 months. Concurrent medication/care: Study was divided into baseline and treatment phases. Patients kept daily seizure records and reported adverse symptoms and medications. Antiepileptic drugs were not changed, except as necessary to maintain appropriate concentrations or in response to apparent drug toxicity. Indirectness: No indirectness Further details: 1. Type of vagus nerve stimulation method:
Funding	Equipment / drugs provided by industry (Supported by a grant from Cyberonics Inc., Webster TX. None of the authors hold sponsor stock or share patent rights or received material support. Some authors received honoraria, received research grants, received consultation fees or gave expert testimony.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HIGH FREQUENCY VAGUS NERVE STIMULATION versus LOW FREQUENCY VAGUS NERVE STIMULATION Protocol outcome 1: Adverse events (lead fracture, infection, hoarse voice, cardiac difficulties, device removal) at N/A - Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Infection at 3 months at 3 months; Group 1: 11/95, Group 2: 12/103 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: withdrawal due to un interpretable dairy, withdrawals (poor compliance, adverse event) ; Group 2 Number missing: 1, Reason: withdrawal of consent - Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Voice alteration at 3 months at 3 months; Group 1: 63/95, Group 2: 31/103 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: withdrawal due to un interpretable dairy, withdrawals (poor compliance, adverse event) ; Group 2 Number missing: 1, Reason: withdrawal of consent	
Protocol outcomes not reported by the study	Quality of life at 12 months at 12 months; Quality of life at 60 months at 60 months; Mortality at 12 months at 12 months; Mortality at 60 months at 60 months; Seizure freedom (100% reduction in seizure frequency) at 12 months at 12 months; Seizure freedom (100% reduction in seizure frequency) at 60 months at 60 months; Seizure frequency (50% or greater reduction in seizure frequency) at 12 months at 12 months; Seizure frequency (50% or greater reduction in seizure frequency) at 60 months at 60 months; Healthcare

Study	Handforth 1998[41]
	resource use at N/A; Social functioning (measures of adaptive functioning or adaptive behaviour using a validated scale) at 12 months at 12 months; Social functioning (measures of adaptive functioning or adaptive behaviour using a validated scale) at 60 months at 60 months; Cognitive outcomes (including neuropsychological measures of global cognitive functioning, executive functioning and memory using a validated scale) at 12 months at 12 months; Cognitive outcomes (including neuropsychological measures of global cognitive functioning, executive functioning and memory using a validated scale) at 60 months at 60 months; In children and young people: neurodevelopmental outcomes (behavioural and emotional outcomes measured with a validated scale) at 12 months at 12 months; In children and young people: neurodevelopmental outcomes (behavioural and emotional outcomes measured with a validated scale) at 60 months at 60 months

Study (subsidiary papers)	Holder 1992[39, 45, 70, 77]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=114)
Countries and setting	Conducted in Canada, Germany, Netherlands, Sweden, USA; Setting:
Line of therapy	1st line
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Children, young people and adults with confirmed pharmacoresistant epilepsy
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients enrolled in the study had medically refractory partially epilepsy. Outpatients or inpatients, aged 12 - 60yrs, males and females, at least 6 seizures/month over a 3 month period, seizures not adequately controlled by AEDs with adequate and stable AED concentrations, simple of complex partial seizures (can evolve to secondarily generalized), ability to understand consent and required study procedure, women using accepted methods of birth control, patients having taken investigational AEDs may be admitted if a

Study (subsidiary papers)	Holder 1992[39, 45, 70, 77]
	period of at least five times the mean elimination half-life of the drug plus 2 weeks have elapsed.
Exclusion criteria	Progressive neurological disease, prior cervical vagotomy, pregnancy, taking more than three antiepileptic drugs, medical condition that is likely to deteriorate or result in hospitalization within the next year.
Age, gender and ethnicity	Age - Mean (range): High group - 34.7 (21.1 - 57.4), low group - 33 (19.7 - 51.4). Gender (M:F): 20 males, 17 females. Ethnicity: N/A
Further population details	1. Children and young people: Not applicable 2. Girls and women of who are able to get pregnant (including those who are pregnant and breastfeeding): Not applicable 3. Older people: Older people 4. People with learning disabilities: 5. Type of epilepsy:
Indirectness of population	No indirectness
Interventions	(n=54) Intervention 1: High frequency vagus nerve stimulation. High frequency - 20 to 50Hz frequency, 500µsec pulse width, 30 to 90µsec on time, 5 to 10 minutes off time.. Duration 12 weeks. Concurrent medication/care: N/A. Indirectness: No indirectness Further details: 1. Type of vagus nerve stimulation method: (n=60) Intervention 2: Low frequency vagus nerve stimulation. Low frequency - 1 to 2 Hz frequency, 130µsec pulse width, 30 seconds on time, 60 to 80 minutes off time. Duration 12 weeks. Concurrent medication/care: N/A. Indirectness: No indirectness Further details: 1. Type of vagus nerve stimulation method:
Funding	Funding not stated (N/A)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HIGH FREQUENCY VAGUS NERVE STIMULATION versus LOW FREQUENCY VAGUS NERVE STIMULATION Protocol outcome 1: Adverse events (lead fracture, infection, hoarse voice, cardiac difficulties, device removal) at N/A - Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Hoarse voice at 12 weeks at 12 weeks; Group 1: 5/20, Group 2: 1/17 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,	

Study (subsidiary papers)	Holder 1992[39, 45, 70, 77]
Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: None died or lost to follow up; Group 2 Number missing: 0, Reason: None died or lost to follow up - Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Infection at 14 weeks at 14 weeks; Group 1: 1/31, Group 2: 2/36 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: None died or lost to follow up; Group 2 Number missing: 0, Reason: None died or lost to follow up - Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Hoarseness at 14 weeks at 14 weeks; Group 1: 11/31, Group 2: 5/36 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: None died or lost to follow up; Group 2 Number missing: 0, Reason: None died or lost to follow up - Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Chest pain at 14 weeks at 14 weeks; Group 1: 2/31, Group 2: 2/36 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: None died or lost to follow up; Group 2 Number missing: 0, Reason: None died or lost to follow up - Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Hypertension at 14 weeks at 14 weeks; Group 1: 0/31, Group 2: 1/36 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: None died or lost to follow up; Group 2 Number missing: 0, Reason: None died or lost to follow up - Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Shortness of breath at 14 weeks at 14 weeks; Group 1: 2/31, Group 2: 0/36 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: None died or lost to follow up; Group 2 Number missing: 0, Reason: None died or lost to follow up - Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Hoarseness at 14 weeks at 14 weeks; Group 1: 20/54, Group 2: 8/60 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: None died or lost to follow up; Group 2 Number missing: 0, Reason: None died or lost to follow up	
Protocol outcomes not reported by the study	Quality of life at 12 months at 12 months; Quality of life at 60 months at 60 months; Mortality at 12 months at 12 months; Mortality at 60 months at 60 months; Seizure freedom (100% reduction in seizure frequency) at

Study (subsidiary papers)	Holder 1992[39, 45, 70, 77]
	12 months at 12 months; Seizure freedom (100% reduction in seizure frequency) at 60 months at 60 months; Seizure frequency (50% or greater reduction in seizure frequency) at 12 months at 12 months; Seizure frequency (50% or greater reduction in seizure frequency) at 60 months at 60 months; Healthcare resource use at N/A; Social functioning (measures of adaptive functioning or adaptive behaviour using a validated scale) at 12 months at 12 months; Social functioning (measures of adaptive functioning or adaptive behaviour using a validated scale) at 60 months at 60 months; Cognitive outcomes (including neuropsychological measures of global cognitive functioning, executive functioning and memory using a validated scale) at 12 months at 12 months; Cognitive outcomes (including neuropsychological measures of global cognitive functioning, executive functioning and memory using a validated scale) at 60 months at 60 months; In children and young people: neurodevelopmental outcomes (behavioural and emotional outcomes measured with a validated scale) at 12 months at 12 months; In children and young people: neurodevelopmental outcomes (behavioural and emotional outcomes measured with a validated scale) at 60 months at 60 months

Study	Michael 1993[61]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=113)
Countries and setting	Conducted in Canada, Germany, Netherlands, Sweden, USA
Line of therapy	1st line
Duration of study	Intervention + follow up: 14 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Children, young people and adults with confirmed pharmacoresistant epilepsy
Subgroup analysis within study	Not applicable
Inclusion criteria	N/A

Study	**Michael 1993[61]**
Exclusion criteria	N/A
Age, gender and ethnicity	Age - Mean (range): 32 (15 - 56). Gender (M:F): N/A. Ethnicity: Not stated.
Further population details	1. Children and young people: 2. Girls and women of who are able to get pregnant (including those who are pregnant and breastfeeding): 3. Older people: 4. People with learning disabilities: 5. Type of epilepsy:
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: High frequency vagus nerve stimulation. High frequency - 1.0 - 3.0 mA output current, 30Hz frequency, 500 microsec pulse width, 30 seconds on time, 5 minutes off time.. Duration 14 weeks. Concurrent medication/care: Patients continued taking antiepileptic drugs and therapeutic serum levels were maintained.. Indirectness: No indirectness Further details: 1. Type of vagus nerve stimulation method: (n=12) Intervention 2: Low frequency vagus nerve stimulation. Low frequency - 0.25 to 0.5 mA output current, 1 hertz frequency, 130 microsec pulse width, 30 seconds on time, 60-90 minutes off time.. Duration 14 weeks. Concurrent medication/care: Patients continued taking antiepileptic drugs and therapeutic serum levels were maintained.. Indirectness: No indirectness Further details: 1. Type of vagus nerve stimulation method:
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HIGH FREQUENCY VAGUS NERVE STIMULATION versus LOW FREQUENCY VAGUS NERVE STIMULATION

Protocol outcome 1: Adverse events (lead fracture, infection, hoarse voice, cardiac difficulties, device removal) at N/A
- Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Hoarseness at 14 weeks at 14 weeks; Group 1: 4/10, Group 2: 5/12
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A

Study	**Michael 1993[61]**
Protocol outcomes not reported by the study	Quality of life at 12 months at 12 months; Quality of life at 60 months at 60 months; Mortality at 12 months at 12 months; Mortality at 60 months at 60 months; Seizure freedom (100% reduction in seizure frequency) at 12 months at 12 months; Seizure freedom (100% reduction in seizure frequency) at 60 months at 60 months; Seizure frequency (50% or greater reduction in seizure frequency) at 12 months at 12 months; Seizure frequency (50% or greater reduction in seizure frequency) at 60 months at 60 months; Healthcare resource use at N/A; Social functioning (measures of adaptive functioning or adaptive behaviour using a validated scale) at 12 months at 12 months; Social functioning (measures of adaptive functioning or adaptive behaviour using a validated scale) at 60 months at 60 months; Cognitive outcomes (including neuropsychological measures of global cognitive functioning, executive functioning and memory using a validated scale) at 12 months at 12 months; Cognitive outcomes (including neuropsychological measures of global cognitive functioning, executive functioning and memory using a validated scale) at 60 months at 60 months; In children and young people: neurodevelopmental outcomes (behavioural and emotional outcomes measured with a validated scale) at 12 months at 12 months; In children and young people: neurodevelopmental outcomes (behavioural and emotional outcomes measured with a validated scale) at 60 months at 60 months
Study	Ryvlin 2014[76]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=96)
Countries and setting	Conducted in Canada, Multiple countries
Line of therapy	1st line
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Children, young people and adults with confirmed pharmacoresistant epilepsy
Subgroup analysis within study	Not applicable

Study	Michael 1993[61]
Inclusion criteria	Eligible participants were 16–75 years old with at least a 2-year history of focal seizures not adequately controlled by ongoing AED therapy. Additional eligibility criteria were (1) previous failure of at least three AEDs used alone or in combination; (2) treatment with at least one AED with a regimen that was stable for at least 1 month prior to study entry; and (3) at least one focal seizure with a motor component per month during the 2 months prior to study entry.
Exclusion criteria	Patients with psychogenic nonepileptic seizures or genetic (idiopathic) generalized epilepsies were not eligible for the study.
Age, gender and ethnicity	Age - Mean (SD): VNS + BMP - 38 (13), BMP - 41 (11). Gender (M:F): 51 male, 45 female. Ethnicity: Not stated.
Further population details	1. Children and young people: 2. Girls and women of who are able to get pregnant (including those who are pregnant and breastfeeding): 3. Older people: Older people 4. People with learning disabilities: 5. Type of epilepsy:
Indirectness of population	No indirectness
Interventions	(n=48) Intervention 1: High frequency vagus nerve stimulation. VNS and best medical practice (BMP) - BMP was defined as the individualized therapy judged optimal by investigators at each visit for each patient, which could include a change in dosage or type of AEDs (including their withdrawal). Clinicians were allowed to adjust VNS stimulation parameters throughout the study. This approach has the advantage of reflecting routine clinical practice, thereby increasing the external validity of the study. Duration 1 year. Concurrent medication/care: All treatments were prescribed and delivered according to the procedures routinely used in clinical practice in each centre. Indirectness: No indirectness Further details: 1. Type of vagus nerve stimulation method: (n=48) Intervention 2: Usual care. Best medical practice - BMP was defined as the individualized therapy judged optimal by investigators at each visit for each patient, which could include a change in dosage or type of AEDs (including their withdrawal). Duration 1 year. Concurrent medication/care: All treatments were prescribed and delivered according to the procedures routinely used in clinical practice in each centre. Indirectness: No indirectness Further details: 1. Type of vagus nerve stimulation method:
Funding	Funding not stated

Study	Michael 1993[61]

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VAGUS NERVE STIMULATION + BMP versus USUAL CARE

Protocol outcome 1: Quality of life at 12 months at 12 months
- Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Quality of Life in Epilepsy Inventory (QOLIE-89) total change score at 1 year at 1 year; Group 1: mean 5.5 (SD 7.2); n=31, Group 2: mean 1.2 (SD 6.9); n=29
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: 2 due to premature study termination, 1 due to consent withdrawal, 1 due to compliance issues, 2 withdrew early for reasons not listed; Group 2 Number missing: 10, Reason: 7 due to premature study termination, 1 due to consent withdrawal, 1 due to compliance issues, 1 due to lack of efficacy

Protocol outcome 2: Seizure frequency (50% or greater reduction in seizure frequency) at 12 months at 12 months
- Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Proportion of people with ≥50% decrease in seizure frequency at 1 year; Group 1: 10/31, Group 2: 7/29
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: 2 due to premature study termination, 1 due to consent withdrawal, 1 due to compliance issues, 2 withdrew early for reasons not listed; Group 2 Number missing: 10, Reason: 7 due to premature study termination, 1 due to consent withdrawal, 1 due to compliance issues, 1 due to lack of efficacy

Protocol outcome 3: Cognitive outcomes (including neuropsychological measures of global cognitive functioning, executive functioning and memory using a validated scale) at 12 months at 12 months
- Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Neurological disorders depression inventory in epilepsy scale (NDDI-E) at 1 year at 1 year; Group 1: mean -1 (SD 2.2); n=31, Group 2: mean -0.2 (SD 3.4); n=29
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: 2 due to premature study termination, 1 due to consent withdrawal, 1 due to compliance issues, 2 withdrew early for reasons not listed; Group 2 Number missing: 10, Reason: 7 due to premature study termination, 1 due to consent withdrawal, 1 due to compliance issues, 1 due to lack of efficacy
- Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Clinical Global Impression of Improvement scale (CGI-I) at 1 year at 1 year; Group 1: mean -0.8 (SD 0.8); n=31, Group 2: mean -0.3 (SD 1.1); n=29
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: 2 due to premature study termination, 1 due to consent withdrawal, 1 due to compliance issues, 2 withdrew early for reasons not listed; Group 2 Number missing: 10, Reason: 7 due to premature study

Study	Michael 1993[61]
termination, 1 due to consent withdrawal, 1 due to compliance issues, 1 due to lack of efficacy Protocol outcome 4: Adverse events (lead fracture, infection, hoarse voice, cardiac difficulties, device removal) at N/A - Actual outcome for Children, young people and adults with confirmed pharmacoresistant epilepsy: Chest pain at 1 year; Group 1: 3/48, Group 2: 0/48 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: 2 due to premature study termination, 1 due to consent withdrawal, 1 due to compliance issues, 2 withdrew early for reasons not listed; Group 2 Number missing: 10, Reason: 7 due to premature study termination, 1 due to consent withdrawal, 1 due to compliance issues, 1 due to lack of efficacy	
Protocol outcomes not reported by the study	Quality of life at 60 months at 60 months; Mortality at 12 months at 12 months; Mortality at 60 months at 60 months; Seizure freedom (100% reduction in seizure frequency) at 12 months at 12 months; Seizure freedom (100% reduction in seizure frequency) at 60 months at 60 months; Seizure frequency (50% or greater reduction in seizure frequency) at 60 months at 60 months; Healthcare resource use at N/A; Social functioning (measures of adaptive functioning or adaptive behaviour using a validated scale) at 12 months at 12 months; Social functioning (measures of adaptive functioning or adaptive behaviour using a validated scale) at 60 months at 60 months; Cognitive outcomes (including neuropsychological measures of global cognitive functioning, executive functioning and memory using a validated scale) at 60 months at 60 months; In children and young people: neurodevelopmental outcomes (behavioural and emotional outcomes measured with a validated scale) at 12 months at 12 months; In children and young people: neurodevelopmental outcomes (behavioural and emotional outcomes measured with a validated scale) at 60 months at 60 months

Appendix E: Coupled sensitivity and specificity forest plots and sROC curves

E.1 High VNS versus Low VNS

Figure 2: Adverse events - infection

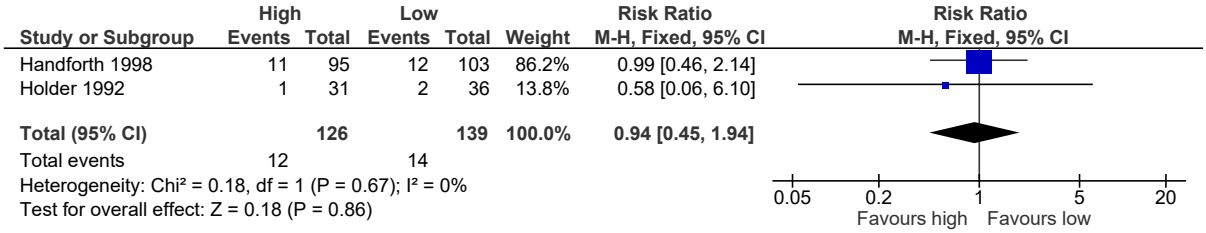


Figure 3: Adverse events - cardiac difficulties (chest pain, shortness of breath)

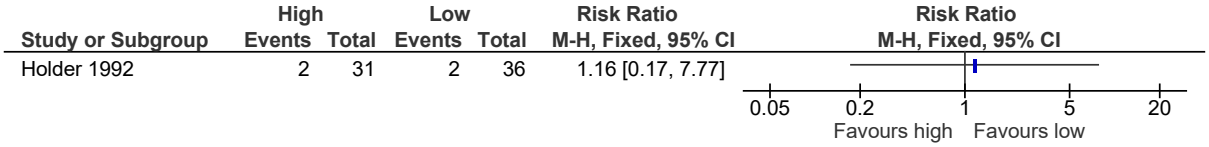
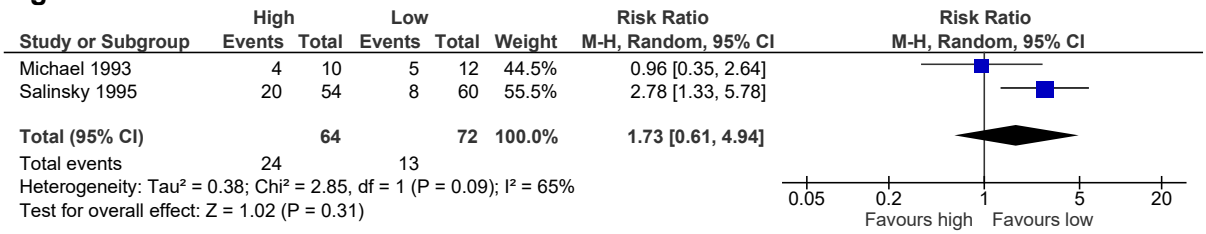


Figure 4: Adverse events - hoarseness



E.2 VNS plus best medical practice versus Best medical practice

Figure 5: Quality of Life in Epilepsy Inventory - 89 (QOLIE-89) scale, 0-89, 1 year, high is good outcome

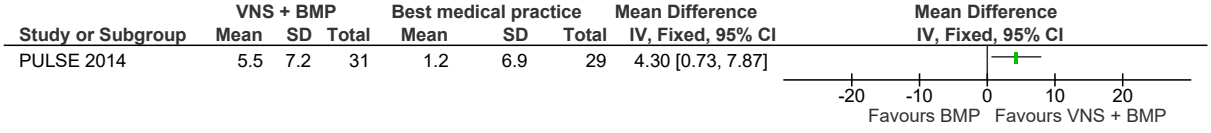


Figure 6: Proportion of people with >50% decrease in seizure frequency, 1 year

Study or Subgroup	VNS + BMP Events	Total	Best medical practice Events	Total	Risk Ratio M-H, Fixed, 95% CI
PULSE 2014	10	31	7	29	1.34 [0.59, 3.04]

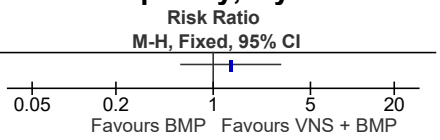


Figure 7: Clinical global impression of improvement scale (CGI-I), 1 year, low is good

Study or Subgroup	VNS + BMP Mean	SD	Total	Best medical practice Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
PULSE 2014	-0.8	0.8	31	-0.3	1.1	29	-0.50 [-0.99, -0.01]

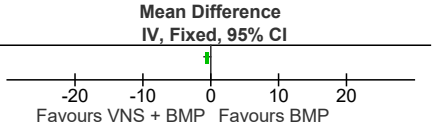


Figure 8: Neurological disorders depression inventory in epilepsy scale (NDDI-E)

Study or Subgroup	VNS + BMP Mean	SD	Total	Best medical practice Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
PULSE 2014	-1	2.2	31	-0.2	3.4	29	-0.80 [-2.26, 0.66]

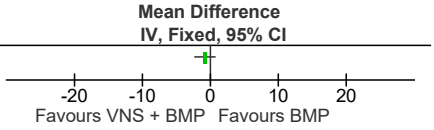
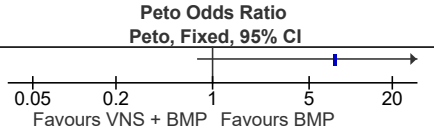


Figure 9: Adverse events - cardiac difficulties (chest pain)

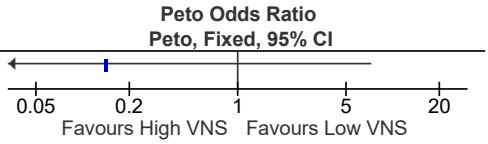
Study or Subgroup	VNS + BMP Events	Total	Best medical practice Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
PULSE 2014	3	48	0	48	7.71 [0.78, 75.97]



E.3 High tVNS versus Low tVNS

Figure 10: Adverse events - Cardiac difficulties

Study or Subgroup	High VNS Events	Total	Low VNS Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Bauer 2016	0	37	1	39	0.14 [0.00, 7.19]



Appendix F:GRADE tables

Table 13: Clinical evidence profile: High VNS versus Low VNS

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High VNS versus Low VNS	Control	Relative (95% CI)	Absolute		
Mortality - not reported												
Seizure freedom - not reported												
Seizure frequency - not reported												
Quality of life - not reported												
Healthcare resource use - not reported												
Adverse events - infection (follow-up 14-16 weeks)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	12/126 (9.5%)	14/139 (10.1%)	RR 0.94 (0.45 to 1.94)	6 fewer per 1000 (from 55 fewer to 95 more)	⊕⊕OO LOW	CRITICAL
Adverse events - cardiac difficulties (chest pain, shortness of breath) (follow-up 14 weeks)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	2/31 (6.5%)	2/36 (5.6%)	RR 1.16 (0.17 to 7.77)	9 more per 1000 (from 46 fewer to 376 more)	⊕OOO VERY LOW	CRITICAL
Adverse events - hoarseness (follow-up 14 weeks)												

2	randomised trials	serious[2]	serious[3]	no serious indirectness	very serious[1]	none	24/64 (37.5%)	13/72 (18.1%)	RR 1.73 (0.61 to 4.94)	132 more per 1000 (from 70 fewer to 711 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[3] Downgraded by 1 or 2 increments because the point estimate and or the confidence intervals varied widely across studies, unexplained by subgroup analysis

Table 14: Clinical evidence profile: VNS + best medical practice versus best medical practice

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**VNS + best medical practice versus best medical practice**	**Control**	**Relative (95% CI)**	**Absolute**		
Mortality - not reported												
Seizure freedom - not reported												
Healthcare resource use - not reported												
Quality of life (follow-up 1 years; measured with: Quality of Life in Epilepsy Inventory - 89 (QOLIE-89) scale; range of scores: 0-89; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	31	29	-	MD 4.3 higher (0.73 to 7.87 higher)	⊕OOO VERY LOW	CRITICAL
Proportion of people with >50% decrease in seizure frequency (follow-up 1 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/31 (32.3%)	7/29 (24.1%)	RR 1.34 (0.59 to 3.04)	82 more per 1000 (from 99 fewer to 492 more)	⊕OOO VERY LOW	CRITICAL
Clinical global impression of improvement scale (follow-up 1 years; measured with: Clinical global impression of improvement scale (CGI-I); Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	31	29	-	MD 0.5 lower (0.99 to 0.01 lower)	⊕OOO VERY LOW	CRITICAL

Neurological outcome (follow-up 1 years; measured with: Neurological disorders depression inventory in epilepsy scale (NDDI-E); Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	31	29	-	MD 0.8 lower (2.26 lower to 0.66 higher)	⊕OOO VERY LOW	CRITICAL
Adverse events - cardiac difficulties (chest pain) (follow-up 1 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/48 (6.3%)	0/48 (0%)	Peto OR 7.71 (0.78 to 75.97)	60 more per 1000 (from 10 fewer to 140 more)	⊕⊕OO LOW	CRITICAL

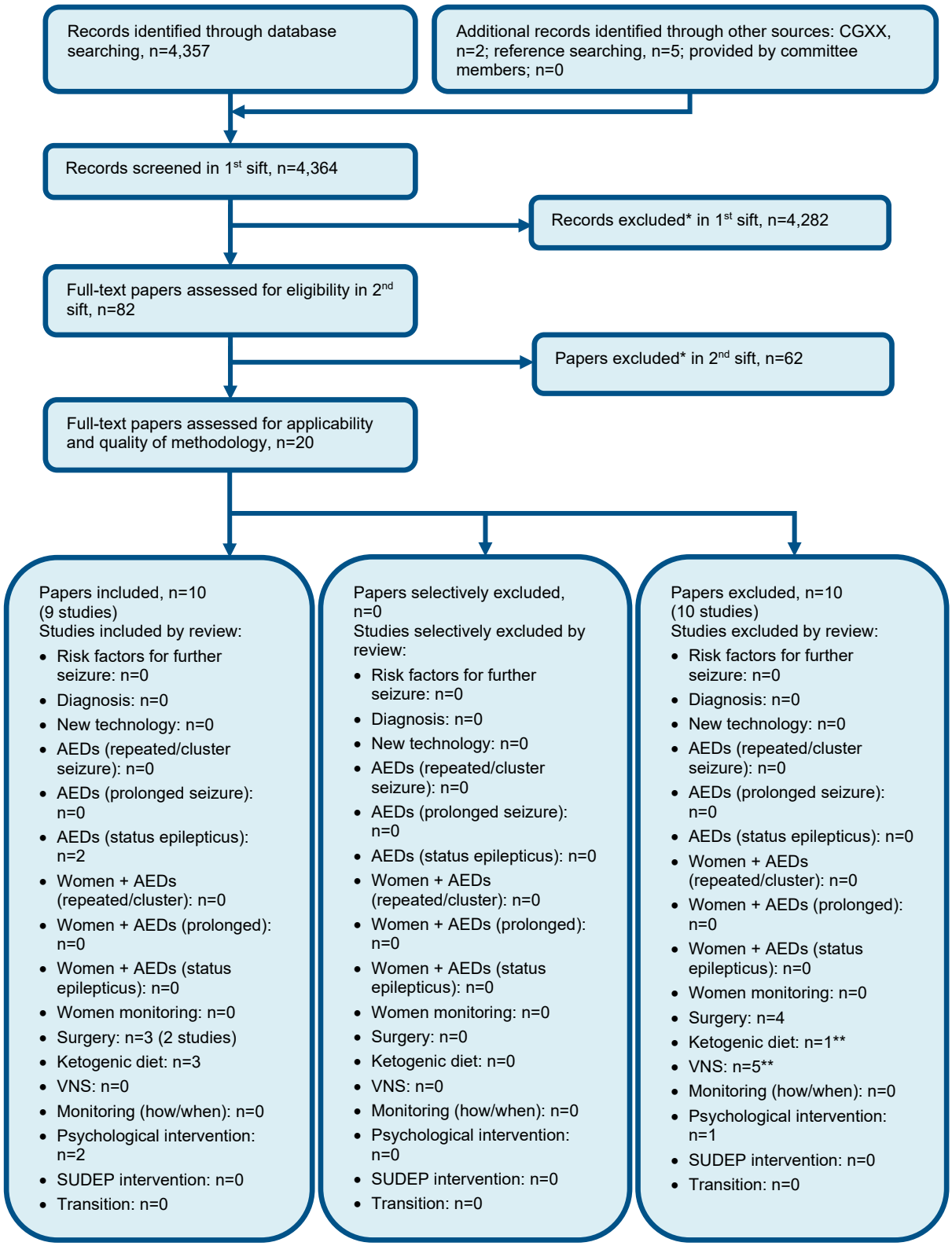
[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 15: Clinical evidence profile: High tVNS versus Low tVNS

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**High tVNS versus Low tVNS**	**Control**	**Relative (95% CI)**	**Absolute**		
Mortality - not reported												
Seizure freedom - not reported												
Seizure frequency - not reported												
Quality of life - not reported												
Healthcare resource use - not reported												
Adverse events - Cardiac difficulties (follow-up 20 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/37 (0%)	1/39 (2.6%)	Peto OR 0.14 (0 to 7.19)	30 fewer per 1000 (from 90 fewer to 40 more)	⊕OOO VERY LOW	

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Appendix G: Health economic evidence selection



* Non-relevant population, intervention, comparison, design or setting; non-English language
**Please note that 1 article related to two questions. For this reason, the numbers listed for each review may not total the number of full text articles assessed for applicability and quality of methodology.

Appendix H: Health economic evidence tables

None

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 16: Studies excluded from the clinical review

Study	Exclusion reason
Aalbers, 2012[1]	Incorrect study design, less than minimum duration. During double blind phase half received high stimulation, half received low, during add on phase all received high.
Aihua, 2014[2]	Incorrect comparisons; Comparing the same tVNS treatment just different stimulation areas - ear lobe or ramsay-hunt zone
Amar, 1998[6]	Less than minimum duration
Amar, 1999[4]	Less than minimum duration
Amar, 1999[5]	Incorrect study design - retrospective
Amar, 2007[3]	Incorrect study design - literature review
Ben-Menachem, 1994[9]	Less than minimum duration
Ben-Menachem, 2002[8]	Incorrect study design - literature review
Bernstein, 2007[10]	Incorrect study design; retrospective study
Boon, 2001[14]	Incorrect study design - case reports
Boon, 2002[13]	Incorrect study design - literature review
Boon, 2009[11]	Incorrect study design - literature review
Broncel, 2017[15]	Incorrect study design; literature review
Bunch, 2007[17]	Incorrect study design - retrospective analysis
Chambers, 2013[18]	Systematic review - references individually checked - not all studies assessed had interventions that met the protocol
Clark, 1999[19]	Incorrect study design; NRS
Clarke, 1997[20]	Incorrect study design - longitudinal double blinded cross over study
Clarke, 1997 [21]	Incorrect study design - longitudinal study
Colicchio, 2010[22]	Incorrect study design -cohort, NRS
Cramer, 2001[23]	Incorrect study design; NRS
Crumrine, 2000[24]	Incorrect study design; Literature review
Cukiert, 2015[25]	Systematic Review: references individually checked
Dasheiff, 2001[26]	Incorrect study design, incorrect comparisons, different objective
DeGiorgio, 2000[28]	Incorrect study design, patients titrated from low stimulation to high stimulation for longer term follow up
DeGiorgio, 2001[29]	Incorrect study design - retrospective analysis of device changes during the E05 study
Dibue-Adjei, 2019[30]	Systematic review - references individually checked - all case reports/case series studies

Study	Exclusion reason
Dodrill, 2001[31]	Less than minimum duration
Elger, 2000[32]	Less than minimum duration
Elliott, 2011[33]	Incorrect study design; retrospective review
Englot, 2011[34]	Systematic review - references checked individually - included study designs that didn't match protocol
Englot, 2016[35]	Incorrect study design - NRS, analysis of registry data
Faught, 2004[36]	Incorrect study design - literature review
Ghani, 2015[40]	Systematic Review: references individually checked
He, 2013[42]	Incorrect study design - cohort
He, 2015[43]	Protocol
Henry, 1998[44]	Incorrect intervention, incorrect comparisons
Hsiang, 1998[46]	Incorrect study design; case series
Ji, 2019[47]	Protocol
Kersing, 2002[48]	Incorrect study design; NRS
Klinkenberg, 2012[49]	Less than minimum duration
Klinkenberg, 2013[51]	Less than minimum duration
Klinkenberg, 2014[50]	Less than minimum duration
Kwan, 2016[54]	Systematic review - references individually checked incorrect population
Labar, 2000[56]	Incorrect study design - literature review
Labar, 2004[55]	Incorrect study design; Literature review
Landy, 1993[57]	Less than minimum duration
Marras, 2013[58]	Incorrect study design - case series, cohort
Marson, 2012[59]	Incorrect study design, incorrect comparisons
McGlone, 2008[60]	Incorrect study design - case control study
Milby, 2009[62]	Incorrect study design, majority of studies listed were not RCTs
Murphy, 1999[63]	Incorrect study design - literature review
Panebianco, 2015[66]	Individual studies assessed - less than minimum follow up duration
Patwardhan, 2000[67]	Incorrect study design - retrospective
Pizzanelli, 2011[68]	Incorrect study design; Cohort study
Privitera, 2002[69]	Individual studies assessed - less than minimum follow up duration
Redgrave, 2018[71]	Systematic Review: references individually checked
Rong, 2014[72]	Less than minimum duration
Rong, 2014[73]	Less than minimum duration
Ryvlin, 2014[74]	Incorrect study design - reference affiliation erratum
Ryvlin, 2015[75]	Incorrect study design - reference affiliation erratum
Salinsky, 1996[79]	Incorrect study design. 1-year open extension trial of blinded RCT (George et al). Blinding was

Study	Exclusion reason
	broken, patients randomised to low were adjusted to high level
Salinsky, 2003[78]	Incorrect study design; Literature review
Scherrmann, 2001[80]	Incorrect study design - NRS
Selner, 2019[81]	Incorrect study design - literature review
Sirven, 2000[82]	Incorrect study design - data from studies we already have (#158 & #116) plus an open label trial
Soleman 2018[83]	Incorrect comparisons; Comparing early vs late implantation (before and after 5 years)
Sourbron, 2017[84]	Systematic Review: references individually checked
Stefan, 2012[85]	Incorrect study design - NRS
Tecoma, 2006 #168;[86]	Incorrect study design; Literature review
Uthman, 1993 #172;	Incorrect study design - single blind, served as their own control
Uthman, 2000[87]	Incorrect study design; Review article
Wheless, 2004[88]	Incorrect study design; Review article
Wiebe, 2006[89]	Systematic review - references checked individually, not all studies assessed VNS, those that did had 3 month follow up
Wilder, 1991[90]	Incorrect study design - case series
Yamamoto, 2015 #178	Incorrect study design - literature review
Zeiler, 2015[91]	Systematic Review: references individually checked

I.2 Excluded health economic studies

Table 17: Studies excluded from the health economic review

Reference	Reason for exclusion
Forbes 2003/2008 [UK][37, 38]	Excluded as rated partially applicable with very serious limitations due to clinical data informing treatment effect based on studies excluded from the clinical review and uncertainty around relevance of cost.
De Kinderen 2015 [Netherlands] [27]	Excluded as rated very serious limitations due to clinical data informing treatment effect based on studies excluded from the clinical review.
Kopciuh 2019/2020 [Poland] [52, 53]	Excluded as rated partially applicable with very serious limitations due to clinical data informing treatment effect based on studies excluded from the clinical review.
Bryant 1998 [UK][16]	This was included in the 2004 guideline but has been excluded because of the date being prior to the date-cut off of 2004, and therefore costs are not applicable.
Boon 1999 [Belgium][12]	This was included in the 2004 guideline, but has been excluded because of the date being prior to the date-cut off of 2004, and therefore costs are not applicable.

Appendix J: Research recommendations

J.1 Effectiveness of vagus nerve stimulation in epilepsy

What is the effectiveness of vagus nerve stimulation in epilepsy? (to include people with learning disabilities as a subgroup)

Why this is important

Around a third of people with epilepsy will not respond to currently available anti-seizure medications. A proportion of this group will be suitable for resective epilepsy surgery. There are, however, people with drug resistant epilepsy who are not candidates for epilepsy surgery or in whom surgery is unsuccessful. In these individuals, alternative methods to control seizures should be considered including neurostimulation or dietary treatments. The clinical effectiveness of these treatments is, though, not well determined.

Rationale for research recommendation

Importance to 'patients' or the population	Although vagal nerve stimulation therapy is performed in people with drug-resistant epilepsy, there are very little robust long-term data to inform the effectiveness of this treatment option. As VNS is an expensive procedure, it is important to critically evaluate the role of VNS in people with epilepsy. Determining who may be most suitable for VNS would allow patient stratification, better counselling of people with epilepsy and potentially be cost-saving.
Relevance to NICE guidance	VNS therapy has been considered in this guideline, and there is a lack of data on long-term clinical and safety outcomes.
Relevance to the NHS	The study would help determine outcomes from VNS and help identify who may be most suitable for VNS. The work may also offer insights into optimal stimulation parameters so that those who receive VNS therapy are enabled to derive the most benefit from the device.
National priorities	Moderate to High (Expensive device; can potentially reduce seizures and mortality; often implanted in those with a learning disability)
Current evidence base	Minimal long-term data on either safety or outcomes. As outcomes from VNS therapy are reported to improve with time, any database/study must include long term follow up for all participants.
Equality considerations	VNS is considered in people with drug-resistant epilepsy who are not thought suitable for resective epilepsy surgery. In clinical practice, VNS is more commonly implanted in those with a learning disability. This research will therefore apply more specifically to people with learning disabilities and enable this population to participate in long-term prospective studies.

Modified PICO table

Population	All people who are considered for VNS implantation who are pharmacoresistant. The threshold for resistance is anyone having seizures despite having drug intervention.
Intervention	VNS (including evaluation of different stimulation parameters) plus best medical care
Comparator	Best medical care
Outcome	Seizure frequency Seizure freedom Mortality Effect on mood Effect on cognition Quality of life (person with epilepsy and family/carers) Adverse device-related outcomes
Study design	Registry/ Case-control study
Timeframe	Long term
Additional information	None